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#### (54) Title: METHODS FOR TREATING GENETICALLY-DEFINED PROLIFERATIVE DISORDERS WITH HSP90 INHIBITORS

Type of Aberration	Background Literature	Affected Gene(s)	Protein Domain	Fusion Protein	<u>Disease</u>
t(9; 22)(q34; q11)	de Klein, A. et al. Nature 300, 765-767 (1982)	CABL (9q34) BCR (22q11)	tyrosine kinase serine kinase	serine + tyrosine kinase	CML/ALL
inv14 (q11; q32)	Bacr, R., Chen, KC., Smith, S. D. & Rabbitts, T. H. Cell 43, 705-713 (1985); Denny, C. T. et al. Nature 320, 549-551 (1986)	TCR-α (14q11) VH-(14q32)	TCR-Cα lg VH	V <sub>H</sub> -TCR-Cα	T/B-cell lymphoma
t(1; 19)(q23; p13.3)	Kamps, M. P., Murre., C., Sun, XH. & Baltimore, D. Cell 60, 547-555 (1990); Nourse, J. et al. Cell 60, 535-545 (1990)	PBX1 (1q23) E2A (19p13.3)	HD AD-b-HLH	AD + HD	pre-B-ALL
t(17; 19)(q22; p13)	Hunger, S. P., Ohyashiki, K. Toyama, K. & Clearly, M. L. Genes Dev. 6, 1608-1620 (1992); Inaba, T. et al. Science 257, 531-534 (1992)	HLF (17q22) E2A (19p13)	PSTIS PSTIS	AD + bZIP	pro-B-ALL
t(15; 17)(q21-q11-22)	Giliard, E. F. & Solomon, E. Sem. Cancer Biol. 4, 359-368 (1993)	PML (15Q21) RARA (17q21)	Zinc-finger Retinoic acid receptor-α	Zinc-finger + RAR DNA and ligand binding	APL
t(11; 17)(q23; q21.1)	Chen, Z. et al. EMBO J. 12, 1161-1167 (1993)	PLZF (11q23) RARA (17q21)	Zinc-finger Retinoic acid receptorα	Zn-finger + RAR DNA and ligand binding	APL
t(4; 11)(q21; q23)	Djabali, M. et al. Nature Genet. 2, 113-118 (1992); Gu, Y. et al. Cell 71, 701-708 (1992)	MLL (11q23) AF4 (4q21)	A-T hook/Zn-finger Set-Pro rich	A-T hook + (Ser-pro)	ALL/preB- ALL/ ANLL
t(9; 11)(q21; q23)	Nakamura, T. et al. Proc. natn. Acad. Sci. U.S.A. 90, 4631-4635 (1993); Lida, S. et al. Oncogene 8, 3085-3092 (1993)	MLL (11q23) AF9/MLLT3 (9p22)	A-T hook/Zn-finger Ser-Pro rich	A-T hook + (Ser-Pro)	ALL/preB- ALL/ ANLL
t(11; 19)(q23; p13)	Tkachuk, D. C., Kohler, S. & Cleary, M. L. Cell 71, 691-700 (1992); Yamamoto, K. et al. Oncogene 8, 2617-2625 (1993)	MLL (11q23) ENL (19p13)	A-T hook/Zn-finger Ser-Pro rich	A-T hook + Scr-Pro	prc-B-ALL/ T-ALL/ ANLL

(57) Abstract: The invention relates generally to methods of treating cell proliferative diseases with HSP90 inhibitors and, depending on the specific aspect and embodiment(s) claimed, to the treatment of proliferative diseases that are associated with fusion proteins, e.g., bcrabl, or mutant proteins or cellular protein isoforms, e.g., mutant forms of p53.



# Methods for Treating Genetically-Defined Proliferative Disorders with HSP90 Inhibitors

#### Field of the Invention

The field of the invention relates to chemotherapeutic treatments of proliferative disorders, including rheumatoid arthritis and neoplasias.

#### **Background of the Invention**

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The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art, or relevant, to the presently claimed inventions, or that any publication specifically or implicitly referenced is prior art.

The eukaryotic heat shock protein 90s (HSP90s) are ubiquitous chaperone proteins that are involved in folding, activation and assembly of a wide range of proteins, including key proteins involved in signal transduction, cell cycle control and transcriptional regulation. HSP90 proteins are highly conserved in nature (see, e.g., NCBI accession # P07900 (SEQ ID NO: 318) and XM 004515(SEQ ID NOs: 319 and 320) (human α and β HSP90, respectively), P11499 (SEQ ID NO: 321) (mouse), AAB23369 (SEQ ID NO: 322) (rat), P46633 (SEQ ID NO: 323) (chinese hamster), JC1468 (SEQ ID NO: 324) (chicken), AAF69019 (SEQ ID NO: 325) (fleshfly), AAC21566 (SEQ ID NO: 326) (zebrafish), AAD30275 (SEQ ID NO: 327)(salmon), AAC48718 (SEQ ID NO: 328) (pig), NP 015084(SEQ ID NO: 329) (yeast), and CAC29071 (SEQ ID NO: 330) (frog).

Researchers have reported that HSP90 chaperone proteins are associated with important signaling proteins, such as steroid hormone receptors and protein kinases, including many that are implicated in tumorigenesis, e.g., Raf-1, EGFR, v-Src family kinases, Cdk4, and ErbB-2 (Buchner J., 1999, TIBS, 24:136-141; Stepanova, L. et al., 1996, Genes Dev. 10:1491-502; Dai, K. et al., 1996, J. Biol. Chem. 271:22030-4). In vivo and in vitro studies indicate that certain co-chaperones, e.g., Hsp70, p60/Hop/Sti1, Hip, Bag1, HSP40/Hdj2/Hsj1, immunophilins, p23, and p50, may assist HSP90 in its function (Caplan, A., 1999, Trends in Cell Biol., 9: 262-68).

Ansamycins are antibiotics derived from Streptomyces *hygroscopicus* which are known to inhibit HSP90s. These antibiotics, *e.g.*, herbimycin A (HA) and geldanamycin (GM), as well as other HSP90 inhibitors such as radicicol, bind tightly to an N-terminal pocket in HSP90 (Stebbins, C. *et al.*, 1997, *Cell*, 89:239-250). This pocket is highly conserved and has weak

1

homology to the ATP-binding site of DNA gyrase (Stebbins, C. et al., supra; Grenert, J.P. et al., 1997, J. Biol. Chem., 272:23843-50). ATP and ADP have been shown to bind this pocket with low affinity, and HSP90 itself has been shown to have weak ATPase activity (Proromou, C. et al., 1997, Cell, 90: 65-75; Panaretou, B. et al., 1998, EMBO J., 17: 4829-36). In vitro and in vivo studies have demonstrated that occupancy of the N-terminal pocket of HSP90 by ansamycins and other inhibitors alters HSP90 function and inhibits client protein folding. At high concentrations, ansamycins and other HSP90 inhibitors have been shown to prevent binding of client protein substrates to HSP90 (Scheibel, T., H. et al., 1999, Proc. Natl. Acad. Sci. USA 96:1297-302; Schulte, T. W. et al., 1995, J. Biol. Chem. 270:24585-8; Whitesell, L., et al., 1994, Proc. Natl. Acad. Sci. USA 91:8324-8328). Ansamycins have also been demonstrated to inhibit the ATP-dependent release of chaperone-associated protein substrates (Schneider, C., L. et al., 1996, Proc. Natl. Acad. Sci. USA, 93:14536-41; Sepp-Lorenzino et al., 1995, J. Biol. Chem. 270:16580-16587), and some of these substrates have been shown to be degraded by a ubiquitin-dependent process in the proteasome (Schneider, C., L., supra; Sepp-Lorenzino, L., et al., 1995, J. Biol. Chem., 270:16580-16587; Whitesell, L. et al., 1994, Proc. Natl. Acad. Sci. USA, 91: 8324-8328).

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This substrate destabilization occurs in tumor and nontransformed cells alike and has been shown to be especially effective on a subset of signaling regulators, e.g., Raf (Schulte, T. W. et al., 1997, Biochem. Biophys. Res. Commun. 239:655-9; Schulte, T. W., et al., 1995, J. Biol. Chem. 270:24585-8), nuclear steroid receptors (Segnitz, B., and U. Gehring. 1997, J. Biol. Chem. 272:18694-18701; Smith, D. F. et al., 1995, Mol. Cell. Biol. 15:6804-12), v-src (Whitesell, L., et al., 1994, Proc. Natl. Acad. Sci. U S A 91:8324-8328) and certain transmembrane tyrosine kinases (Sepp-Lorenzino, L. et al., 1995, J. Biol. Chem. 270:16580-16587) such as EGF receptor (EGFR) and Her2/Neu (Hartmann, F., et al., 1997, Int. J. Cancer 70:221-9; Miller, P. et al., 1994, Cancer Res. 54:2724-2730; Mimnaugh, E. G., et al., 1996, J. Biol. Chem. 271:22796-801; Schnur, R. et al., 1995, J. Med. Chem. 38:3806-3812). The ansamycin-induced loss of these proteins leads to the selective disruption of certain regulatory pathways and results in growth arrest at specific phases of the cell cycle (Muise-Heimericks, R. C. et al., 1998, J. Biol. Chem. 273:29864-72), and apoptsosis of cells so treated (Vasilevskaya, A. et al., 1999, Cancer Res., 59:3935-40).

Growth arrest of this sort, provided it can be made selective, has important ramifications for the treatment of certain proliferative disorders, including cancer. Whereas cancer treatments have thus far been limited to traditional surgical removal, radiation, and/or chemotherapy, and

whereas these procedures have been more or less successful, a need remains to develop additional therapies with increased efficacy and decreased side-effects that can be used alone or in combination with existing therapies. There particularly remains a need for cancer treatments that target specific cancer types. The present invention satisfies these needs and provides related advantages as well.

### **Summary of the Invention**

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Applicants report that many proliferative disorders are associated with aberrant proteins that exhibit a dependence on HSP90. In some cases this dependence manifests as a heightened sensitivity to HSP90 inhibitors such that affected cells can be selectively treated using a dosage that is effective against the aberrant cells but which is ineffective or less effective against normal cells. The aberrant proteins may also exhibit increased proteosome-dependent degradation when in the presence of HSP90 inhibitors. While the invention is not limited by mechanism, increased dependence, sensitivity, and /or disposition to preferential degradation may advantageously be used to treat corresponding proliferative diseases according to the methods of the invention.

Among others, the invention targets two groups of aberrant proteins in particular and the corresponding proliferative disorders they are associated with. Within the first group are fusion proteins generated as a result of non-random chromosomal aberrations (such as translocations, deletions and inversions) that juxtapose parts of the coding sequences of two normal cellular proteins (Rabbitts, T., 1994, *Nature* 372:143-149). Duplication of genetic material within a chromosome resulting in a augmented or semi-duplicative transcripts is also a possibility. Within the second group are mutants and isoforms of cellular proteins that override, dominate, or otherwise obscure the natural gene products and their function. For example, mutants and isoforms of p53 family proteins and other tumor suppressor gene products can act as dominant-negative inhibitors of the corresponding normal protein in heterozygous tumor cells (Blagosklonny, M., *et al.*, 1995, *Oncogene*, 11:933-939. Other examples include virally-encoded species of certain kinases, such as v-src and other dominantly-acting mutant oncogene products (Uehara, Y. *et al.*, 1985, *supra*).

Accordingly, in a first aspect the invention features a method of treating a patient having a genetically-defined proliferative disease characterized by a non-random chromosomal aberration. This aberration produces or is capable of producing an oncogenic fusion protein. The method in its broadest embodiment includes (a) providing a

3

cell, tissue, or fluid sample of a patient suspected of having a genetically-defined proliferative disease; (b) identifying in the cell, tissue, or fluid sample one or more characteristics indicative of the proliferative disease; and (c) administering to the patient a pharmaceutically effective amount of an HSP90-inhibiting compound.

The patient may be any organism that can manifest a proliferative disease characterized by an oncogenic fusion protein, which disease is responsive to HSP90 inhibitors. Preferably, but not necessarily, the organism is an animal, more preferably a mammal, and most preferably a human.

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In preferred embodiments, the inhibitory compound is an ansamycin including but not limited to, e.g., geldanamycin, the geldanamycin derivative, 17-AAG, herbimycin A, and/or macbecin. Most preferably, the ansamycin is 17-AAG. These and other ansamycins and methods of preparing them are well-known in the art. See, e.g., US Patents 3,595,955, 4,261,989, 5,387,584, and 5,932,566. Although preferably the compound is an ansamycin, the method may make use of any compound, synthetic or nonsynthetic, that can inhibit HSP90. Preferably, the inhibitor binds the ATP-binding site of HSP90, or an HSP90 homolog. Radicicol is a nonsynthetic example of a compound useful in the invention described and claimed herein. Libraries of small molecules, synthetic and/or nonsynthetic exist or can be made according to routine, well-known methods and screened for HSP90 binding and/or inhibitory activity. These molecules with HSP90 binding and/or inhibitory activity are also useful in the methods of the invention.

In the identifying step of the invention, which is carried out prior to diagnosis where/when there is no previous diagnosis, any technique can be used that can identify or predict a proliferative disorder targetable by HSP90 inhibitors. Especially preferred are antibody-based and nucleic acid hybridization and/or amplification techniques.

Immunoprecipitation, western blotting, and immunoblotting are illustrative examples of antibody-based methods. The antibodies may be monoclonal and/or polyclonal.

Illustrative examples of nucleic acid hybridization-based techniques involve Southern blotting, northern blotting, and dot-blotting. Illustrative examples of nucleic acid amplification include standard polymerase chain reactions and variations thereof, e.g., reverse transcriptase-PCR (RT-PCR). The latter is especially useful for identifying levels of gene expression. Other techniques such as the ligase chain reaction (LCR) are also

well-known and have the ability to distinguish an aberrant gene (and indirectly a protein product produced therefrom) from a normal one, or at least predict genotype and/or phenotype. Other methods of identification include ligand-binding assays and gel-retardation assays that display characteristic binding affinities and/or mobility profiles for normal and variant proteins. Where the fusion protein is also an enzyme, one can establish and/or measure aberrance by enzymatic activity (or lack thereof). Conventional and derivative karyotyping and cytochemical techniques can also be used to identify a proliferative disorder of the invention prior to administration of HSP90-inhibitors. One such method is fluorescent *in situ* hybridization (FISH).

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In some embodiments, the proliferative disease is a hematopoietic disorder including but not limited to one selected from the group consisting of T or B cell lymphomas, chronic myeloid leukemias (CMLs), acute promyelocytic leukemias (APLs), acute lymphoid or lymphoblastic leukemias (ALLs), acute myeloid leukemias (AMLs), non-Hodgkin lymphomas (NHLs), and chronic myelomonocytic leukemias (CMMLs). In other embodiments, the disease is characterized by a solid tumor, preferably including but not limited to papillary thyroid carcinoma, Ewing's sarcoma, melanoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma. The embodiments are not necessarily mutually exclusive of one another, and treatment of multiple distinct diseases may simultaneously be effected in a given patient, as the invention has broad-spectrum merit against a variety of different proliferative disorders.

Targeted fusion proteins may contain one or more functional domains or portions thereof, e.g., kinases, DNA binding motifs, etc. Such domains are well-known in the art. Figure 1 illustrates several types of these domains, and the specific fusion proteins, genes, and diseases they can be associated with.

Administration may be by a variety of means. In some preferred embodiments, administration is made *ex vivo*, *e.g.*, removing and treating blood or tissue that is thereafter administered back into the patient. Alternatively, or in combination, administration may be intralesional, *e.g.*, administered to the site of a solid tumor, and/or parenteral. These constitute just some of the many different modes of administration that can be used. Others are described herein.

In other embodiments, the HSP90-inhibiting compound has an IC<sub>50</sub> that is higher (preferably two-fold, more preferably five-fold, and most preferably ten-fold) for cells that do not have characteristics indicative of the proliferative disorder as compared with those cells that do have such characteristics.

In other embodiments, the patient may be tested pre- and/or post-administration for sensitivity and or effect of one or more HSP90 inhibitors. This may be done *in vitro* or *in vivo*.

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Numerous non-random chromosomal aberrations exist that are associated with proliferative disorders. These include but are not limited to chromosomal translocations, inversions, and deletions. Duplications also account for some aberrant chromosomes and aberrant resulting gene products. All aberrations can be targeted in various aspects of the invention. Illustrative examples of specific aberrations include those listed in Figure 1, which is adapted from Table 1 of Rabbitts, Nature 372:143-149 (1994), and others including but not limited to: inv14 (q11; q32), t(9; 22)(q34; q11), t(1; 19)(q23; p13.3), t(17; 19)(q22; p13), t(15; 17)(q21-q11-22), t(11; 17)(q23; q21.1), t(4; 11)(q21; q23), t(9; 11)(q21; q23), t(11; 19)(q23; p13), t(X; 11)(q13; q23), t(1; 11)(p32; q23), t(6; 11)(q27; q23), t(11; 17)(q23; q21), t(8; 21)(q22; q22), t(3; 21)(q26; q22), 5(16; 21)(p11; q22), t(6; 9)(p23; q34), 9; 9?, t(4; 16)(q26; p13), inv(2; 2)(p13; p11.2-14), inv(16)(p13q22), t(5; 12)(q33; p13), t(2; 5)(2p23; q35), t(9:12)(q34:p13), del(12p), t(9;22),+8,+Ph,i(17q), t(15;17)(q22;q12), t(11;17)(q23;q12), t(16:16)(p13;q22), inv(16)(p13;q22), t(9;11)(p22;q23), t(1;22)(p13;q13), t(3;3)(q21;q26), inv(3)(q21q26), t(3;5)(q21;q31), t(3;5)(q25;q34), t(7;11)(p15;p15), t(8;16)(p11;p13), t(9;12)(q34;p13), t(12;22)(p13;q13),del(5q), del(7q), del(20q), t(11q23), t(12;21)(p13;q22), t(5;12)(q31;p13), t(1;12)(q25;p13), t(12;15)(p13;q25), t(1;12)(q21;p13), t(12;21)(q13;p32), and t(5;7)(q33;q11.2). These are merely a sampling of the many chromosomal aberrations well-known in the art that give rise to particular proliferative disorders treatable according to the invention. For these and others, see, e.g., the National Center for Biotechnology Information (NCBI) databases, including, e.g., the Online Mendelian Inheritance in Man (OMIM) database and related links to nucleotide and protein sequences. For purposes of the present invention, the underlying genetic sequences affected are for the most part known and/or may be deduced using techniques routine in the art.

Targeted in particularly preferred embodiments of the invention are chromosomal aberrations corresponding to t(9; 22)(q34; q11) that give rise to bcr-abl fusion proteins, chronic myelogenous leukemia (CML) and, in some cases, acute lymphoid or lymphoblastic leukemia (for ALL, see, e.g., Erikson et al., Heterogeneity of chromosome 22 breakpoint in Philadelphia-positive (Ph+) acute lymphocytic leukemia, Proc. Nat. Acad. Sci. 83: 1807-1811 (1986))).

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In a second aspect, the invention features a method of treating cancerous cells in a heterogeneous population of cells. The heterogeneous population includes both cancerous and noncancerous cells, and the cancerous cells are further characterized by fusion proteins that are not produced in the noncancerous cells. The method includes administering to the heterogeneous population a pharmaceutically effective amount of an HSP90-inhibiting compound. The population may be tested by separation of samples from each population into separate subpopulations, cancerous or noncancerous, *e.g.*, where cultured cells of each are tested in parallel for response and/or susceptibility to an HSP90-inhibitor or candidate inhibitor molecule. Alternatively, the population may be mixed, *e.g.*, in an *ex vivo* procedure in which cells of a patient, *e.g.*, blood, are treated and administered back to the patient or to another individual. This method otherwise tracks the various described and/or claimed embodiments and/or combinations of embodiments of the first aspect.

In a third aspect, the invention features a method of treating a patient having a proliferative disease associated with a mutant protein or cellular protein isoform dependent on HSP90, or which disease is otherwise sensitive to HSP90 inhibitors. The method includes (a) providing a cell, tissue, or fluid sample of a patient suspected of having said proliferative disease; (b) identifying in the cell, tissue, or fluid sample one or more characteristics indicative of a mutant or cellular protein isoform; and (c) administering to the patient a pharmaceutically effective amount of an HSP90-inhibiting compound.

In preferred embodiments, the mutant protein or cellular protein isoform is selected from the group consisting of src, RET, p53, p51, p63, and p73. Most preferably selected are isoforms of p53 selected from N239S, C176R, and R213\*, Y236delta, C174Y, M133T, G245D, E258K, 1-293delta, G245C, R248W, E258K, R282W, R175H, R280K,

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V143A, R175H, P177S, H178P, H179R, R181P, 238-9delta, G245S, G245D, M246R, R248Q, R249S, R273H, R273C, R273L, and D281Y.

In another preferred embodiment, the proliferative disease to be treated is rheumatoid arthritis.

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In some embodiments, the mutant protein or cellular protein isoform may give rise to a dominant negative phenotype. In other embodiments, the mutant or cellular protein isoform may give rise to a dominant positive mutant. In either embodiment, the patient may be heterozygous for the normal cellular gene. Other embodiments track those listed for the preceding aspects.

In a fourth aspect, the invention features a method of selectively treating cells that express a mutant protein or cellular protein isoform associated with a proliferative disorder and which mutant/isoform is dependent on HSP90, or which disease is otherwise sensitive to HSP90 inhibitors. The method includes (a) providing a population of cells in which at least some of the population express a mutant protein or cellular protein isoform that is dependent on HSP90 or which are otherwise sensitive to HSP90 inhibitors. The method further includes administering to the population a pharmaceutically effective amount of an HSP90-inhibiting compound. The embodiments for this aspect may otherwise track preceding embodiments.

The foregoing aspects contemplate treatment of existing cell proliferative disorders. It is expected that the invention may also find use in prophylactic prevention of various proliferative disorders of the invention. Further, and where appropriate, each of the embodiments discussed above and different combinations thereof, including subgenus and sub-Markush groups, may cross-apply to each of the different aspects of the invention. Further, where sequence listings are provided, the invention may in some aspects contemplate subsequences of the primary sequence listings. Any subsequence within such primary listing is also contemplated for the invention, as well as all allelic variants, and mutant variants and isoforms thereof, as well as corresponding homologs from other organisms and species. Sequences contiguous with and/or in addition to the listed sequences and their above equivalents are also contemplated.

Advantages of the invention include broad-acting treatment or prophylaxis directed to a variety of different proliferative disorders. Other advantages include the efficient and rapid diagnosis and care of patients suffering from proliferative disorders, with minimal apparent adverse effects. Still other advantages, aspects, and embodiments will be apparent from the figures, the detailed description, and the claims.

### **Brief Description of the Drawings**

Figure 1 illustrates various genetically defined diseases characterized by non-random chromosomal aberrations that give rise to oncogenic fusion proteins. These illustrative aberrations, diseases, and fusion proteins are targeted in various embodiments of the invention. Other targeted aberrations, diseases, and fusion proteins may be found in the specification and in sources commonly known in the art, e.g., the NCBI and GenBank databases, and journal literature.

### **Detailed Description of the Invention**

# **Definitions**

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As used herein and in the claims the following terms have the following meanings:

A "genetically-defined disease" is one with a basis in DNA. Genetically defined diseases of the invention include "cell proliferative disorders" wherein unwanted cell proliferation of one or more subset(s) of cells in a multicellular organism occurs, resulting in harm, for example, pain or decreased life expectancy to the organism. "Cell proliferative disorders" refer to disorders wherein unwanted cell proliferation of one or more subset(s) of cells in a multicellular organism occurs, resulting in harm, for example, pain or decreased life expectancy to the organism. Cell proliferative disorders include, but are not limited to, cancers, tumors, benign tumors, blood vessel proliferative disorders, autoimmune disorders and fibrotic disorders. These disorders are not necessarily independent. For example, fibrotic disorders may be related to, or overlap with, blood vessel disorders, *e.g.*, atherosclerosis (which is characterized herein as a blood vessel disorder that is associated with the abnormal formation of fibrous tissue).

A "non-random chromosomal aberration" is one that occurs with a nonrandom frequency or is selected for in a population of individuals. Chromosomal aberrations of the invention include translocations, *i.e.*, relocation of a fragment of one chromosome onto another

chromosome; inversions, *i.e.*, wherein pieces of a chromosome rotate within the same chromosome, and deletions, *i.e.*, wherein fragments of a chromosome are lost thereby juxtaposing pieces of DNA that previously did not reside immediately beside each other.

An "oncogenic fusion protein" is a protein that is non-natural in and of itself but that may contain one or more pieces of other proteins that may or may not naturally occur within a cell. The fusion protein functions by improperly stimulating cell growth, directly or indirectly. In the context of the invention, the term is also associated with a cellular proliferative disease and is preferably encoded by a nucleic acid found in the cell, *e.g.*, as part of a non-random chromosomal aberration. An oncogenic fusion protein may contain domains or portions thereof, *e.g.*, kinases and/or DNA binding proteins that are well known in the art, or else predicted from their structure to behave as such.

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A "fusion" may relate to, as appropriate to a given context, a fusion chromosome, an abnormal mRNA transcribed from the fused portion of the chromosome, or a polypeptide product translated from the abnormal mRNA that is transcibed from the fusion chromosome. These fusions may result from chromosomal deletions, insertions, and/or translocations. Domains or portions of different genes and gene products are frequently, although not necessarily always, brought together as a consequence of the fusion event. For example, an intragenic deletion can result in an intragenic fusion and give rise to an abnormal protein lacking a component from a second gene. More frequently it occurs that two genes or portions thereof are juxtaposed more or less, transcribed together as a single transcript, and translated together as a fusion protein bearing contributions from multiple genes or other chromomosal DNA pieces. In such fusions, reading frames can be preserved, e.g., as in preserved functional domains or portions thereof coming from two or more different genes, or else the reading frame can be disrupted, e.g., as in the case of a "missense" or "nonsense" event as these terms are known in the art.

By "providing a cell, tissue, or fluid sample of a patient suspected of having said genetically-defined disease" and "identifying one or more characteristics indicative of said disease in or on said cell, tissue, or fluid sample" can mean, although is not limited to the situation where, the sample is withdrawn from the patient in order to perform the analysis or analyses. Many invasive and noninvasive procedures exist, e.g., NMR, ultrasound and other imaging techniques, that can be used to diagnose, at least in part, an illness and its cause. For example, "tagged" antibodies or other ligands with affinity for a fusion protein or chromosomal aberrancy or

aberrancy product of the invention can be used to make the diagnosis and/or assist in treatment according to methods of the invention.

"Characteristics indicative of said disease" may embrace phenotypes or genotypes and may be measured qualitatively or quantitatively by a variety of techniques. The characteristics may be observed with the naked eye or else through the assistance of a machine or other diagnostic technique(s). Exemplary techniques of measurement include but are not limited to immunoreactivity and/or precipitation, PCR, LCR, karyotyping, and fluorescence activated cell sorting ("FACS)" as those terms are known and understood in the art.

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"Administering" can be by direct means, e.g., intralesional or by parenteral or peripheral administration to a patient, or else by indirect means, e.g., as by withdrawing a patient's cells, treating them, and then re-introducing them back into the patient. The latter constitutes an "ex vivo" technique.

An "HSP90-inhibiting compound" is one that disrupts the expression, structure, and/or function of an HSP90 chaperone protein and/or a protein that is dependent on HSP90. HSP90 proteins are highly conserved in nature (see, *e.g.*, NCBI accession #'s P07900 and XM 004515 (human α and β HSP90, respectively), P11499 (mouse), AAB2369 (rat), P46633 (chinese hamster), JC1468 (chicken), AAF69019 (flesh fly), AAC21566 (zebrafish), AAD30275 (salmon), O02075 (pig), NP 015084 (yeast), and CAC29071 (frog). There are thus many different HSP90s, all with anticipated similar effect and similar inhibition capabilities. The HSP90 inhibitor used in the methods of the invention may be specifically directed against an HSP90 of the specific host patient or may be identified based on reactivity against an HSP90 homolog from a different species, or an artificial HSP90 variant. The inhibitors used may be ring-structured antibiotics, *e.g.*, benzoquinone ansamycins, or other types of molecules, *e.g.*, antisense nucleic acids and molecules such as radicicol.

An "ansamycin" includes but is not limited to geldanamycin, 17-AAG, herbimycin A, and macbecin. The specific ansamycin 17-AAG stands for 17-allylamino-17-demethoxygeldanamycin. This and other ansamycins that can be used are well-known in the art. *See, e.g.*, U.S. Patent Nos. 3,595,955, 4, 261, 989, 5,387,584, and 5,932,566. Ansamycins may be synthetic, naturally-occurring, or else derivatives of naturally occurring ansamycins that are prepared using standard chemical derivatization techniques.

A "pharmaceutically effective amount" means an amount which is capable of providing a therapeutic or prophylactic effect. The specific dose of compound administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the specific compound administered, the route of administration, the condition being treated, the individual being treated, and the tissue or cell type targeted (or not targeted). A typical daily dose (administered in single or divided doses) will contain a dosage level of from about 0.01 mg/kg to about 100 and more preferaby 50 mg/kg of body weight of an active compound of this invention. Preferred daily doses generally will be from about 0.05 mg/kg to about 20 mg/kg and ideally from about 0.1 mg/kg to about 10 mg/kg.

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A preferred therapeutic effect is the inhibition to some extent of the growth of cells causing or contributing to a cell proliferative disorder. A therapeutic effect will also normally, but need not, relieve to some extent one or more of the symptoms of a cell proliferative disorder other than cell growth or size of cell mass. In reference to the treatment of a cancer, a therapeutic effect refers to one or more of the following: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (*i.e.*, slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 3) inhibition (*i.e.*, slowing to some extent, preferably stopping) of tumor metastasis; 4) inhibition, to some extent, of tumor growth; and/or 5) relieving to some extent one or more of the symptoms associated with the disorder.

In reference to the treatment of a cell proliferative disorder other than a cancer, a therapeutic effect refers to either: 1) the inhibition, to some extent, of the growth of cells causing the disorder; 2) the inhibition, to some extent, of the production of factors (e.g., growth factors) causing the disorder; and/or 3) relieving to some extent one or more of the symptoms associated with the disorder.

With respect to viral infections, the preferred therapeutic effect is the inhibition of a viral infection. More preferably, the therapeutic effect is the destruction of cells which contain the virus.

A "cancer" refers to one or more various types of benign or malignant neoplasms. In the case of the latter, these may invade surrounding tissues and may metastasize to different sites, as defined in Stedman's Medical Dictionary 25th edition (Hensyl ed. 1990).

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The term " $IC_{50}$ " is defined as the concentration of an HSP90 inhibitor required to achieve killing or other growth inhibition of 50% of the cells of a homogenous cell type population, or of a particular cell type, *e.g.*, cancerous versus noncancerous, over a period of time. The  $IC_{50}$  is preferably, although not necessarily, greater for normal cells than for cells exhibiting a proliferative disorder.

The term "mutant or isoform cellular protein" refers to a variation of a wild-type protein that occurs in a cell and has a particular function. The mutant or isoform cellular protein of the invention preferably associates with or gives rise to a proliferative disorder, *e.g.*, a cancer, whereas the wild-type protein ordinarily does not.

#### 10 General

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As described and claimed herein, ansamycins and other HSP90 inhibitors can be used to treat two important classes of tumor-promoting (oncogenic) human proteins.

### 1. Oncogenic Fusion Proteins

The first class of target proteins of the invention are fusion proteins generated as a result of non-random chromosomal aberrations (such as translocations, deletions and inversions) that juxtapose parts of the coding sequences of two normal cellular proteins (Rabbitts, T., 1994, *Nature* 372:143-149) leading to the lineage-specific expression of a mutant fusion protein that has biological activities derived from both parent proteins (Barr, F, 1998, *Nat. Genet.* 19:121-124). Without being limiting of the invention, Applicants have discovered that these fusion proteins have a heightened dependence on HSP90 chaperone activity, and/or decreased stability in the presence of HSP90 inhibitors, thus making them selective targets for treatment with HSP90 inhibitors.

#### a. Bcr-abl as an example

One example of heightened HSP90 dependence and inhibitor sensitivity is observed when chronic myelogenous leukemia (CML) cells harboring the fusion oncoprotein p210-bcr-abl are treated with HSP90 inhibitors. This fusion protein is degraded faster and more completely than wild type c-abl protein (An, W et al, 2000, Cell Growth and Differentiation 11: 355-360). Further experimental evidence that bcr-abl expressing leukemia cells are more sensitive to HSP90 inhibitors than are closely related bcr-abl-negative leukemia lines is found in Honma, Y et al,

1995, *Int. J. Cancer* 60:685-688, where it is reported that the IC<sub>50</sub> of herbimycin A in six bcr-abl expressing leukemia cell lines averaged 29.3 nM as compared to a mean IC<sub>50</sub> of 399.3 nM in a panel of four bcr-abl-negative leukemia lines. Illustrative protein and nucleic acid sequences corresponding to embodiments of bcr-abl fusions of the invention include but are not limited to those found in SEQ ID NOs 1-26 and subsequences thereof, which are further discussed below, along with corresponding NCBI accession numbers.

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The normal Bcr gene occupies a region of about 135 kb on chromosome 22. It is expressed as mRNAs of 4.5- and 6.7-kb, which apparently encode for the same cytoplasmic 160-kD protein, and contains 23 exons as well as an unusual inverted repeat flanking the first exon. The BCR protein reportedly contains a unique serine/threonine kinase activity and at least two SH2 binding sites encoded in its first exon and a Cterminal domain that functions as a GTPase activating protein for p21(rac) (Diekmann et al., Nature 351: 400-402 (1991). Chissoe et al., Genomics 27: 67-82 (1995), sequenced the complete BCR gene and greater than 80% of the human ABL gene, which are both involved in the t(9:22) translocation (Philadelphia chromosome) associated with more than 90% of chronic myelogenous leukemia, 25 to 30% of adult and 2 to 10% of childhood acute lymphoblastic leukemia, and rare cases of acute myelogenous leukemia. Comparison of the gene with its cDNA sequence revealed the positions of 23 BCR exons and putative alternative BCR first and second exons. From the sequence of four newly studied Philadelphia chromosome translocations and a review of several other previously sequenced breakpoints, Chissoe et al. found a variety of breakpoints and recombinations sites possible within the genes. Thus, despite the normal chromosomes and genes each being known (9 and 12; bcr and abl), and the fact that combinations of these genes are known to lead to forms of CML and ALL, the precise genetic breakpoint/recombination junctions that lead to these diseases can vary.

This heterogeneity likely also applies to some non bcr-abl chromosomal aberrations of the invention as well. Nevertheless, because the genes and/or chromosomes involved are known to have a part in the disorders, the disorders are said to be "genetically defined."

#### b. Other oncogenic fusion proteins

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Oncogenic fusion proteins in general are thought to be inherently unstable. To the extent these unstable oncogenic fusion proteins make use of HSP90, they are susceptible of the methods claimed herein. Because the fusion genes and their protein products exert overtly oncogenic activity (Deininger, M et al, 2000, Cancer Res. 60:2049-2055), preferential degradation of these labile proteins induced by HSP90 inhibitors will have therapeutic value in diseases where the fusion protein is expressed. The present invention thus includes treatment of patients with tumors that are dependent upon other oncogenic fusion proteins that arise from non-random genetic aberrations. An illustrative but nonexhaustive list of these tumors is included in Figure 1, adapted from Table 1 of Rabbitts, T., 1994, Nature 372:143-149. The list may be supplemented by additional information found, e.g., in Rowley, J, 1999, Semin. Hematol. 36:59-72 and other publications known in the art, as well as discussion below.

Myeloid cancers in particular are within the scope of the invention and include chromosomal abnormalities that give rise to oncogenic fusion proteins that drive the growth of chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), and acute lymphoblastic leukemia (ALL). The following chromosomal aberrancies give rise to some illustrative fusions implicated in various forms of ALL:

t(1:19)(q23:p13) Pro-pre-B acute lymphoblastic leukemia
t(12:21)(p13:q32) Pro-pre-B acute lymphoblastic leukemia
t(9:22)(q34:q11) B or B-myeloid acute lymphoblastic leukemia
t(9:12)(q34:p13) Acute B-lymphoblastic leukemia
del(12p) Acute B-lymphoblastic leukemia

Specific genes and proteins thereof implicated in various ALL forms include the *MLL* gene and the *TEL* gene, which are commonly rearranged in tumors. Rowley, J, *supra*. Each has numerous fusion partners. ETV6 denotes the name of the TEL gene product. Fusion of TEL/ETV6 to an acyl CoA synthetase, ACS2, results from a t(5;12)(q31;p13) AML event(Yagasaki, F *et al*, 1999, *Genes Chromosomes Cancer* 26:192-202); fusion of TEL/ETV6 to ABL-related gene (ARG)

results from a t(1;12)(q25;p13) AML event (Iijima, Y et al, 2000, Blood 95:2126-2131); fusion of TEL/ETV6 to the neurotrophin-3 receptor TRKC results from a t(12;15)(p13;q25) AML event and gives rise to congenital fibrosarcoma (Liu, Q et al, 2000, EMBO J. 19:1827-1838, Eguchi, M et al, 1999, Blood 93:1355-1363); fusion of TEL/ETV6 to the aryl hydrocarbon receptor ARNT results from a t(1;12)(q21;p13) event and gives rise to acute myeloblastic leukemia (AML-M2) (Salomon-Nguyen, F et al, 2000, Proc. Natl. Acad. Sci. 97:6757-6762); and fusion of TEL/ETV6 to AML-1, the DNA-binding subunit of the AML-1/CBFb transcription factor results from a (12;21)(q13;p32) event that can give rise to acute lymphoblastic leukemia (ALL, Shurtleff, SA et al, 1995, Leukemia 9:1985-1989) and, in some cases, non-Hodgkin's lymphoma (NHL).

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Another illutrative fusion within the scope of the invention is the EWS/FLI-1 hybrid protein that is the hallmark of Ewing's sarcoma and the primitive neuroectodermal tumor family (Silvany, *et al*, 2000, *Oncogene* 19:4523-4530).

Yet another illustrative family of fusion proteins within the scope of the invention is the group of fusion proteins arising from chromosomal rearrangements involving the *RET* gene in thyroid cancer (Kolibaba, K, *et al*, 1997, *Biochem. Biophys. Acta* 1333:F217-F248).

Rearrangements of *RET*, resulting in juxtaposition of the RET tyrosine kinase domain with one of three 5' sequences (RET-PTC-1, -2 and -3) generate fusion proteins comprising the kinase domain of RET fused to parts of the genes *H4* (RET-PTC-1), *R1a* of cAMP-dependent protein kinase A (RET-PTC-2) and ELE-1 (RET-PTC-3).

The scope of the present invention also includes cancers and other proliferative diseases, e.g., rheumatoid arthritus, now known or discovered in the future to be characterized by specific chromosomal aberrations giving rise to fusion proteins.

In at least some cases, heterogeneity of breakpoints within the affected chromosomes is possible, thus providing for the possibility of many different DNA fusions and amino acid sequence variations than those specifically listed in the SEQ ID NOs provided, and which can also be formed by the chromosomal rearrangements, e.g., translocations, inversions, deletions, insertion/duplications, etc., so designated. For example, many different abl-bcr gene combinations and corresponding fusion proteins can be designated by the t(9; 22)(q34; q11) translocation event, and all—not just those listed below—are included within the purview of the designation, t(9;22)(q34;q11).

Aberrant proteins of the invention, at least in some instances, feature one or more properties of the individual normal parent genes' gene products (normal polypeptide gene product(s), including e.g., functional and structural domains and subportions thereof resulting from transcription and translation of normal parent genes on normal chromosomes) but otherwise lack exact identity and function with the parent genes' protein products. Chromosomal aberrations may give rise to in-frame fusions or frameshifts, the latter of which can account for missense or nonsense translation of at least a portion of the mRNA, and thereby result in aberrant polypeptide product(s).

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Of the SEQ ID NOs discussed herein, some reflect fusion genes, some reflect fusion gene products, e.g., mRNAs and peptides, and some reflect portions of such entities. Still some others reflect recombination "hot spots" in the normal genes that have a general propensity to form a chromosomal aberration. Each of the above sequences may be useful as diagnostic markers in appropriate embodiments of the invention and/or may be characteristic of a given proliferative disorder (or patient exhibiting such and, accordingly, a candidate for treatment according to some methods of the invention.

While the specific sequences discussed are predominantly human in origin, it is understood that other animal "homologs" of the corresponding human sequences are known in the art and are intended to be within within the purview of various aspects of the invention. Because HSP90s are also found in plants, plants and plant cells and tissues exhibiting fusion protein products that give rise to undesirable traits may also be treatable in some aspects and embodiments of the invention. The NCBI nucleotide and protein databases are an example of where such sequences can be found. It is also appreciated that the complete human genome and other genomes have been sequenced, and continue to be sequenced at a hight rate, thus facilitating the identity of sequences contiguous with those listed herein and homologs thereto.

Further, some of the sequences listed herein may contain errors associated with the logistical complexities of compiling such extensive data, and the true sequences should be interpreted to be within the scope of the invention, either literally or under the doctrine of equivalents, as they are known in the art.

As those of ordinary skill will appreciate, allelic variations and different isotype proteins are also possible for some genes, e.g., the product of differential splicing events in

mRNA, and these are likewise considered within the scope of the invention. Further, some of the NCBI and SEQ ID NOs listed below are for wild-type genes, and are included to give an indication of the different chimeric possibilities for the fused counterpart during a chromosomal aberration according to the invention. Should any of the sequences listed below be in error, such should be construed consistent with what is commonly understood in the art—irrespective of how presented in the application.

### c. Further Discussion of Illustrative Chromosomal Aberrancies

Convention: where two or more SEQ ID NOs are provided per NCBI accession #, peptide(s) shall be listed first where applicable, followed by corresponding mRNA/cDNA and/or genomic sequence as the case may be. The terms "nucleotide" and "nucleotides" are interchangeable with, and may be symbolized by, "nt."

## t(9; 22)(q34; q11)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S72478, corresponding to SEQ ID NOs 1 and 2, illustrates one aberrant polypeptide/mRNA in a patient having CML and another patient having ALL. The junction for the nucleic acid sequence between the BCR and ABL genes is stated to reside between nucleotides 100 and 101., with 1-100 derived from BCR and 101-140 derived from ABL.

NCBI #M19695 (SEQ ID NO 3) illustrates a nucleic acid sequence identified from a human myelocytic chimeric bcr/chromosome 9 fusion (CML K562 cell line).

NCBI #M30829 (SEQ ID NOs 4 and 5) illustrates a partial bcr/abl fusion protein mRNA.

NCBI #M13096 (SEQ ID NO 6) illustrates a human chimeric bcr/c-abl fusion protein gene characteristic of cell line K562.

NCBI #M30832 (SEQ ID NOs 7 and 8) corresponds to a human bcr/abl fusion protein, partial cds, clone E3 from cell line EM2.

NCBI # AJ131466 (SEQ ID NOs 9 and 10) corresponds to a partial human ber/abl (major breakpoint) fusion peptide and the underlying nucleic acid encoding it.

Nucleotides 1-373 are said to derive from exons 11-14 of the ber gene, and nucleotides 374-997 are said to derive from exons 2-4 of the abl gene.

NCBI # AF192533 (SEQ ID NOs 11 and 12) corresponds to a partial human bcr/abl (major breakpoint) fusion mRNA. Nucleotides 1-289 are said to come from the bcr gene of chromosome 22 and nucleotides 290-305 from the able gene of chromosome 9.

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NCBI # AF321981 (SEQ ID NO 13) corresponds to a BCR-ABL fusion transcript e15a2 mRNA sequence. This particular fusion is stated to result from results from a translocation between the 3' portion of the c-ABL oncogene on chromosome 9 and exon 15 of the BCR gene on chromosom22; t(9;22).

NCBI # M17543 (SEQ ID NO 14) corresponds to at least a portion of a Philadelphia chromosome breakpoint cluster region associated with one embodiment of a bcr abl fusion gene. Nucleotides 1-31 are said to be exon 1 and nucleotides 32-63 are said to be intron A.

NCBI # M17542 (SEQ ID NOs 15 and 16) corresponds to a human bcr/abl fusion protein mRNA (product of translocation t(22q11; 9q34)), exons 1 and 2. Nucleotides 1-31 are stated to denote exon 1 and nucleotides 32-63 are stated to denote exon 2.

NCBI # M17541(SEQ ID NOs 17 and 18) corresponds to a human bcr/abl fusion protein mRNA (product of translocation t(22q11; 9q34)), exons 1 and 2. Nucleotides 1-31 are stated to denote exon 1 and nucleotides 32-63 are stated to denote exon 2.

NCBI # AB069693 (SEQ ID NOs 19 and 20) denotes a human partial mRNA corresponding to a bcr/abl e8a2 fusion protein. BCR exons 7 (nucleotides 1-53) and 8 (nucleotides 54-194) are joined to ABL intron1b inverted (nucleotides 195-249) and ABL exon a2 (nucleotides 250-423).

NCBI # AJ131467(SEQ ID NOs 21 and 22) correspond to a human partial BCR/ABL chimeric fusion peptide and corresponding mRNA. Nucleotides 1-117 denote exon 1 of the bcr gene, nucleotides 118-193 and 194-298 denote exons 12 and 13 of the

ber gene, and nucleotides 299-472, 473-768, and 769-922 respectively denote exons 2-4 of the abl gene.

NCBI # AF113911 (SEQ ID NOs 23 and 24) correspond to a partial BCR-ABL minor breakpoint peptide (BCR-ABL fusion) mRNA. Nucleotides 1-455 are stated to be from chromosome 22 and nucleotides 456-1079 from chromosome 9.

NCBI # AF251769 (SEQ ID NOs 25 and 26) correspond to a human partial bcr/abl e1-a3 chimeric fusion protein (BCR/ABLe1-a3) mRNA. Nucleotides 1-455 are stated to be from chromosome 22 and nucleotides 456-1079 from chromosome 9.

### inv14 (q11; q32)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # X82240 (SEQ ID NOs 27 and 28) correspond to at least a portion of an mRNA for the gene TCL1, which is disrupted in aberrations of the type noted.

NCBI # NM\_021966 (SEQ ID NOs 29 and 30) relate to a human T-cell leukemia/lymphoma 1A (TCL1A), mRNA.

NCBI # X82241 (SEQ ID NO 31) relates to a 5' portion of a human TCL1 gene. Nucleotides 496-560 are said to correspond to exon 1.

NCBI # M14198 (SEQ ID NOs 32 and 33) relate to a human chromosome 14 paracentric inversion producing an heavy chain/T-cell receptor J-alpha fusion protein.

NCBI # X03752 (SEQ ID NOs 34 and 35) relate to a human gene for rearranged Ig V(H) are said to encode the IgVH region (108 aa) and nucleotides 324 to 377 are said to encode 18 amino acids of the TCR-J-alpha protein.

NCBI # M12071 (SEQ ID NOs 36 and 37) relates to a human Ig heavy-chain V-region gene (VII family) rearranged to T-cell receptor alpha-chain D-J-sp region (IgT) in an inv(14)(q11; q32), SUP-T1 cell line. Nucleotides 121-166 are said to derive from exon 1 of the IgH gene, nucleotides 167-248 from intron 1 of the IgH gene, nucleotides 249-623 from exon 2 of the IgH gene, and nucleotides 624-675 from intron 2 of the IgH gene.

NCBI # S45947 (SEQ ID NOs 38 and 39) relate to an IgT=T cell specific exon ET-immunoglobulin VH-T cell receptor J alpha fusion [human, T cell lymphoma cell line SUP-T1, mRNA Mutant, 508 nt]. Nucleotides 34-507 are stated to be IgT coding sequence.

NCBI # S45207 (SEQ ID NOs 40 and 41) relate to an IgT=T cell specific exon ET-exon EX-immunoglobulin VH-T cell receptor J alpha fusion [human, T cell lymphoma cell line SUP-T1, mRNA Mutant, 616 nt]. Nucleotides 130-616 are stated to be IgT coding sequence.

### t(1; 19)(q23; p13.3)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # M31522 (SEQ ID NOs 42 and 43) relate to a human translocation (t1;19) fusion protein (E2A/PRL) mRNA, 3' end. ]. Nucleotides 1-1653 are stated to encode a portion of an E2A/PRL fusion protein.

### t(17; 19)(q22; p13)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # M95586 (SEQ ID NOs 44 and 45) relate to a human E2A/HLA fusion protein (E2A/HLF) mRNA, complete cds. Nucleotides 31-1755 are said to be coding sequence.

### t(15; 17)(q21-q11-22)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S50916 (SEQ ID NOs 46 and 47) relate to a PML-RAR fusion gene {fusion transcript} [human, mRNA Partial, 1284 nt]. Nucleotides 1-1251 are said to be coding sequence.

NCBI # M73779 (SEQ ID NOs 48 and 49) relate to a human PML-RAR protein (PML-RAR) mRNA, complete cds; coding sequence: nucleotides 67-2460.

NCBI # AJ417079 (SEQ ID NOs 50 and 51) relate to a human partial mRNA for PML/RARA fusion protein (PML/RARA gene); Nucleotides 1-109 derive from exon 6 of PML, nucleotides 110-172 from intron 2 of RARA, and nucleotides 173-296 from exon 3 of RARA.

### t(11; 17)(q23; q21.1)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # AAB29813 (SEQ ID NO 52) relates to a retinoic acid receptor alpha, RAR alpha(PLZF=zinc finger protein, PLZF-RAR alpha isoform A=fusion protein) {translocation} [human, acute promyelocytic leukemia patient, Peptide Mutant, 858 aa].

NCBI # AAB29814 (SEQ ID NO 53) relates to a PLZF=zinc finger protein(retinoic acid receptor alpha, RAR alpha, RAR alpha 1-PLZF isoform B=fusion protein) {translocation} [human, acute promyelocytic leukemia patient, Peptide Mutant, 277 aa].

### t(4; 11)(q21; q23)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # L22179 (SEQ ID NOs 54 and 55) relate to a human MLL-AF4 der(11) fusion protein mRNA, complete cds. Nucleotides 5-6940 are said to be coding sequence.

NCBI # S67825 (SEQ ID NOos 56 and 57) relate to a human ALL1-AF4 fusion protein mRNA, partial cds. Nucleotides 1-585 are said to derive from chromosome 11 and nucleotides 586-832 from chromosome 4.

NCBI # AF024541 (SEQ ID NOs 58 and 59) relate to a human MLL-AF4 fusion protein mRNA, partial cds. The codons are said to start with nucleotide 3.

NCBI # AF031404 (SEQ ID NOs 60 and 61) relate to a human MLL-AF4 fusion protein mRNA, partial cds. Nucleotides 1-305 are said to derive from chromosome 11 and nucleotides 306-741 from chromosome 4. Codons begin with nucleotide 3.

NCBI # L04731 (SEQ ID NO 63) relates to a human translocation T(4:11) of the human ALL-1 gene to chromosome 4.

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NCBI # AF177237 (SEQ ID NOs 64 and 65) relate to human cell-line MV4-11, MLL/AF4 fusion protein (MLL/AF4) mRNA, partial cds. Nucleotides 1-62 derive from exon 6 of the MLL gene on chromosome 11, and nucleotides 63-450 from exon 5 of the AF4 gene on chromosome 4.

NCBI # AF177236 (SEQ ID NOs 66 and 67) relate to a human A1 MLL/AF4 fusion protein (MLL/AF4) mRNA, partial cds. Nucleotides 1-63 are stated to derive from exon 6 of the MLL gene on chromosome 11, and nucleotides 64-450 from exon 5 of the AF4 gene on chromosome 4.

NCBI # AF031403 (SEQ ID NO 68) relates to a human MLL/AF4 translocation breakpoint t(4;11)(q21;23). Nucleotides 1-105 are said to derive from exon 5 of MLL, nucleotides 435-508 from exon 6 of MLL, nucleotides 2195-2326 from exon 7 of MLL, nucleotides 2874-2987 from exon 8 of MLL, and nucleotides 3645-6983 from AF4.

NCBI # AF177238 (SEQ ID NOs 69 and 70) relate to a human A1 AF4-MLL fusion protein (AF4-MLL) mRNA, partial cds. Nucleotides 1-484 are said to derive from exon 3 of AF4 and nucleotides 485-596 from exon 7 of MLL.

NCBI # AF177239 (SEQ ID NOs 71 and 72) relate to a human cell-line MV4-11 AF4-MLL fusion protein (AF4-MLL) mRNA, partial cds. Nucleotides 1-484 are said to derive from exon 3 of AF4 and nucleotides 485-596 from exon 7 of MLL

NCBI # AF397907 (SEQ ID NO 73) relates to a human AF4/MLL translocation breakpoint region. Nucleotides 1-437 are said to derive from intron 3 of AF6, nucleotides 440-631 from intron 6 of MLL, and nucleotides 632-747 from exon 7 of MLL. The breakpoint is approximately nucleotide 438-439, which was undetermined due to GC compressions.

NCBI # AF024543(SEQ ID NO 74) relates to a human MLL/AF4 translocation breakpoint t(4;11)(q21;q23).

# t(9; 11)(q21; q23)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S82034 (SEQ ID NO 75) relates to an MLL-AF9=fusion gene {fusion site} [human, peripheral blood, acute myeloid leukemia FAB type M1 patient UPN 427, mRNA Partial, 60 nt].

### t(11; 19)(q23; p13)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S81007 (SEQ ID NO 76) relates to an MLL/ENL=fusion gene {rearranged derivative 11 junction region} [human, leukemic lymphoblasts, T-cell acute lymphoblastic leukemia patient RUPN2, Genomic Mutant, 74 nt]. The authors indicated that the first 34 nt derived from MLL intron 8 on 11q23, and nt 35-74 from the ENL-distal region on 19p13.3

NCBI # S81008 (SEQ ID NO 77) relates to an ENL {rearranged derivative 19 junction region} [human, leukemic lymphoblasts, T-cell acute lymphoblastic leukemia patient RUPN2, Genomic Mutant, 84 nt]. The authors indicated that nt 55-84 derived from MLL gene 3' region on 11q23.

### t(X; 11)(q13; q23)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # NM\_005938 (SEQ ID NOs 78 and 79) relate to a human myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 7 (MLLT7), mRNA. Nucleotides 183-1688 denote an MLLT7 coding

region, with nucleotides 465-719 and 480-749 corresponding to a forkhead and forkhead domain, and G and C allelic variations possible at nucleotide 1435.

NCBI # X93996 (SEQ ID NOs 80 and 81) relate to a human mRNA for AFX protein. Nucleotides 183-1688 are said to be AFX coding sequence.

### 5 t(1; 11)(p32; q23)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # AF331760 (SEQ ID NO 82) relates to human clone UPN5379L mRNA sequence (bone marrow acute lymphoblastic FAB L2 type).

### 10 t(6; 11)(q27; q23)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S82519 (SEQ ID NOs 83 and 84) relate to a human MLL-AF6 fusion protein mRNA, partial cds, identified in a leukemic patient, and with the breakpoint stated to be approximately between nt 26 and 27.

NCBI # S82521 (SEQ ID NOs 85 and 86) relate to a an MLL-AF6=fusion gene {breakpoint region, clone b} [human, blood, leukemic patient 2, mRNA Partial, 69 nt]. The breakpoint here is said to reside between nt 24 and 25.

NCBI # S82517 (SEQ ID NOs 87 and 88) relate to an MLL-AF6=fusion gene {breakpoint region} [human, blood, leukemia patient 1, mRNA Partial, 69 nt]. The breakpoint here is said to reside between nt 24 and 25.

### t(11; 17)(q23; q21)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S72604 (SEQ ID NOs 89 and 90) relate to an AF17...ALL-1 {reciprocal translocation} [human, acute myeloid leukemia patient, mRNA Partial Mutant, 3 genes,

228 nt]. Nucleotides 1-88 are said to derive from AF17 and nucleotides 89-228 from ALL-1.

NCBI # (SEQ ID NOs 91 and 92) relate to a human myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 6 (MLLT6), mRNA. Nucleotides approximating 22-168 are said to encode a PHD zinc finger motif and nucleotides 2185-2292 (amino acids 729-764) are said to encode a leucine zipper motif, with A and G allelic variations at nt 592 possible.

### t(8; 21)(q22; q22)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI# (SEQ ID NOs 93 and 94) relate to a human mRNA for AML1-MTG8 fusion protein, complete cds. The coding sequence is said to be nucleotides 1579-3837 and the breakpoint is said to be between nt 2110 and 2111.

NCBI # S78158 (SEQ ID NOs 95 and 96) relate to a human AMLI-ETO fusion protein (AML1-ETO) mRNA, partial cds. Nucleotides 1-1767 are said to denote the coding sequence.

NCBI # S78159 (SEQ ID NOs 97 and 98) relate to a human AML1-ETO fusion protein (AML1-ETO) mRNA, partial cds. . Nucleotides 1-696 are said to denote the coding sequence and nucleotides 40 and 41 are said to represent the junction point.

NCBI # D14822 (SEQ ID NOs 99 and 100) relate to a human chimeric partial mRNA derived from AML1 and MTG8(ETO) gene sequences. Nucleotides 1-101 are said to derive from the AML1 gene on chromosome 21 and nucleotides 102-799 from the MTG8 (ETO) gene on chromosome 8.

NCBI # S45790 (SEQ ID NO 101) relates to a AML1/ETO=acute myelogenous leukemia {translocation breakpoint} [human, Genomic Mutant, 237 nt].

NCBI # Z35296 (SEQ ID NO 102) relates to a human AML1/ETO alternative fusion transcript mRNA, 276bp. Nucleotides 1-117 are said to derive from AML1 and 186-276 are said to derive from ETO.

NCBI # D14823 (SEQ ID NOs 103 and 104) relate to a human chimeric mRNA derived from AML1 gene and MTG8(ETO) gene, partial sequence. Nucleotides 1-101 are said to be derived from the AML1 gene on chromosome 21 and nucleotides 102-1446 are said to be derived from the MTG8(ETO) gene on chromosome 8, with the coding sequence denoted at 1-757.

# t(3; 21)(q26; q22)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S69002 (SEQ ID NOs 105 and 106) relate to a AML1-EVI-1=AML1-EVI-1 fusion protein {rearranged translocation} [human, leukemic cell line SKH1, mRNA Mutant, 5938 nt]. The author indicated the boundary between AML1 and EVI-1 to be between nt 2138 and 2139, with the coding sequence being 1603-5790.

NCBI # L21756 (SEQ ID NOs 107 and 108) relate to a human acute myeloid leukemia associated protein (AML1/EAP) mRNA, complete cds. Nucleotides 1-786 are said to denote the coding sequence.

NCBI # S76343 (SEQ ID NO 109) relates to AML1...EAP {translocation breakpoint} [human, chronic myelogenous leukemia in blast crisis patient, Genomic Mutant, 3 genes, 470 nt]. Nucleotides 1-125 are said to derive from AML1 and nucleotides 126-470 are said to derive from EAP.

### 20 t(16; 21)(p11; q22)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S71718 (SEQ ID NOs 110 and 111) relate to a TLS/FUS...ERG {translocation} [human, myeloid leukemia patient, peripheral blood, bone marrow cells, mRNA Partial Mutant, 3 genes, 55 nt]. Nucleotides 46-55 are said to derive from ERG, with the codon start beginning with nt 3.

NCBI # S71805 SEQ ID NOs 112 and 113) relate to a TLS/FUS...ERG {translocation} [human, myeloid leukemia patient, peripheral blood, bone marrow cells,

mRNA Partial Mutant, 3 genes, 99 nt]. Nucleotides 1-89 are said to derive from TLS/FUS and nucleotides 90-99 from ERG, with the codon start beginning with nt 3.

NCBI # Y10001(SEQ ID NO 114) relates to a DNA fragment containing fusion point of FUS gene and ERG gene, translocation t(16;21)(p11;q22).

### 5 **t(6; 9)(p23; q34)**

NCBI # X64229 (SEQ ID NOs 115 and 116) relate to a human dek mRNA. The coding sequence is said to be nt 34-1161.

### inv(9;9)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # X63689 (SEQ ID NO 117) relates to a human translocation breakpoint in the "can" gene sequence. The translocation breakpoint is said to be 174..175.

NCBI # M93651 (SEQ ID NOs 118 and 119) relate to a human set gene, complete cds. The coding sequence is said to be 4-837.

### 15 **t(4; 16)(q26; p13)**

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # Z14955 (SEQ ID NOs 120 and 121) relate to a human mRNA encoding the interleukin 2/BCM fusion protein. Nucleotides 1-321 derive from exons 1-3 of IL-2 and nucleotides 322-864 from the BCM gene.

### inv(16)(p13q22)

This inversion is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # AF251768 (SEQ ID NOs 122 and 123) relate to a human PCBFB/MYH11E chimeric fusion protein (CBFB/MYH11) mRNA, partial cds.

Nucleotides 1-41 correspond to exon 5 of CBFB and nucleotides 42-78 to exon 7 of MYH11.

NCBI # AF249898 (SEQ ID NOs 124 and 125) relate to a human PCBFbeta/MYH11A chimeric fusion protein (CBFbeta/MYH11A) mRNA, partial cds. Nucleotides 1-41 correspond to exon 5 of CBFB and nucleotides 42-102 to exon 12 of MYH11.

NCBI # AF249897 (SE ID NOs 126 and 127) relate a human PCBFb-MYH11d chimeric fusion protein (CBFB/MYH11D) mRNA, partial cds. Nucleotides 1-41 correspond to exon 5 of CBFB and nucleotides 42-109 to exon 8 of MYH11.

NCBI # AF390860 (SEQ ID NO 128) relates to a human isolate UPN2 CBFB/MYH11 translocation breakpoint region sequence.

NCBI # AF390859 (SEQ ID NO 129) relates to a human isolate UPN1 CBFB/MYH11 translocation breakpoint region sequence.

NCBI # AF202996 (SEQ ID NOs 130 and 131) relate to human core binding factor beta-smooth muscle myosin heavy chain fusion protein (CBFB-MYH11) mRNA, partial cds. Nucleotides 1-46 are said to correspond to 16q22 and nucleotides 47-89 to 16p13. Nucleotide 50 is said to be a "t" in some cases.

### t(5; 12)(q33; p13)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # NM\_001987 (SEQ ID NOs 132 and 133) relate to a human ets variant gene 6 (TEL oncogene) (ETV6), mRNA. Nucleotides 25-1383 are said to correspond to coding sequence, of which nt 136-393 are said to correspond to a sterile alpha motif (SAM) pointed domain, nt 1036-1290 to an erythroblast transformation-specific (Ets)-domain, and wherein allelic variations including "c"s and "t"s at each of nt 798, nt 1541, and nt 1598, and an "a"s and "c"s at each of nt 1822 and 1881.

NCBI # U11732 (SEQ ID NOs 134 and 135) relate to a human ets-like gene (tel) mRNA, complete cds. The coding sequence is said to be from nt 25-1383, and the translocation breakpoint said to occur after nt 487.

### t(2; 5)(2p23; q35)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI #14: AF032882 (SEQ ID NO 136) relates to a human anaplastic lymphoma kinase receptor (ALK) and nucleophosmin (NPM) truncated genes at a t(2;5) translocation breakpoint. Nucleotides 1-46 are said to be ALK sequence that is truncated at 3' due to translocation, and nucleotides 1370-1451 are said to be NPM sequence that is truncated at 5' due to translocation.

NCBI # S82740 (SEQ ID NO 137) relates to a NPM/ALK=fusion gene {translocation breakpoint} [human, lymphoma cells SUP-M2, Genomic, 1565 nt].

NCBI # S82725 (SEQ ID NO 138) relates to a NPM/ALK=fusion gene {translocation breakpoint} [human, lymphoma cells SU-DHL-1, Genomic, 1679 nt].

NCBI # U04946 SEQ ID NOs 139 and 140) relate to a human nucleophosminanaplastic lymphoma kinase fusion protein (NPM/ALK) mRNA, complete cds. The recombination junction is said to occur at nt 353.

### t(11; 22) (q24; q12)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # AJ229320 (SEQ ID NO 141) relates to a human translocation t(11;22) DNA in ewings's tumor derivative 22 (isolate: EWTUM64/ MIC). Nucleotides 1-88 are said to denote EWS sequence and nucleotides 89-180 FLI-1 sequence.

NCBI # AJ229311 SEQ ID NO 142) relates to a human translocation t(11;22) DNA in ewings's tumor derivative 22 (isolate: EWTUM56/EW20). Nucleotides 1-114 are said to denote EWS sequence and nucleotides 115-180 FLI-1 sequence.

NCBI # AF177752 (SEQ NO 143) relates to a human clone Jugo Ewing's sarcomaspecific EWS-FLI1 chimera target sequence.

NCBI # AF177751 (SEQ ID NO 144) relates to a human Juyon Ewing's sarcomaspecific EWS-FLI1 chimera target sequence.

NCBI # AF177750 (SEQ ID NO 145) relates to a human clone Iti Ewing's sarcoma-specific EWS-FLI1 chimera target sequence.

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NCBI # AF327066 SEQ ID NOs 146 and 147) relate to a human Ewings sarcoma EWS-Fli1 (type 1) oncogene mRNA, complete cds.

NCBI # XM\_060745 (SEQ ID NOs 148 and 149) relate to a human similar to
EWS/FLI1 activated transcript 2 (H. sapiens) (LOC127935), mRNA. Nucleotides 10-225
and 13-195 are said to denote src homology 2 (SH2) domains.

NCBI # AF403479 SEQ ID NOs 150 and 151) relate to a human EWS/FLI1 activated transcript 2 protein mRNA, complete cds.

NCBI # AF020264 (SEQ ID NOs 152 and 153) relate to a human EWS/FLI1 activated transcript 2 homolog (EAT-2) gene, partial cds.

NCBI # AF020263 (SEQ ID NOs 154 and 155) relate to a Mus musculus EWS/FLI1 activated transcript 2 (EAT-2) mRNA, complete cds.

NCBI # S72620 SEQ ID NOs 156 and 157) relate to a EWS...Fli1 [human, T93-113 tumor, mRNA Partial Mutant, 3 genes, 229 nt]. Nucleotides 1-85 are said to denote partial EWS gene sequence and nt 86-229 are said to denote partial FLI-1 sequence.

NCBI # S64709 (SEQ ID NO 158) relates to EWS...Fli-1 {translocation} [human, IARC-EW11 Ewing's tumor-derived cells, mRNA Mutant, 3 genes, 100 nt]. Nucleotides 1-18 are said to denote partial EWS gene sequence and nt 19-100 are said to denote partial FLI-1 sequence.

NCBI # S62665 (SEQ ID NOs 159 and 160) relate to a type 4 EWS-FLI1 fusion {translocation} [human, primitive neuroectodermal tumor cell line TC-32, mRNA Partial Mutant, 60 nt]. Positions 1-31 are said to be from the 5' portion of EWS on chromosome

22 and positions 32-60 are said to be from the 3' (DNA-binding) region of FLI1 on chromosome 11.

### inv(10)(q11.2; q21)

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This aberration is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # AF395885 (SEQ ID NO 161) relates to a human H4/RET fusion mRNA, partial sequence, tyrosine kinase domain of the ret. Nt 1-83 are said to derive from H4, nt 84-142 from an unidentified insertion sequence, and nt 143-447 from ret. The tyrosine kinase domain in the ret portion is said be constitutively active in the fusion product.

NCBI # NM\_005436 (SEQ ID NOs 162 and 163) relate to a human DNA segment, single copy, probe pH4 (transforming sequence, thyroid-1, (D10S170), mRNA. Nt 37-1794 are said to represent coding sequence, nt 202-996 said to encode a mysosin tail, nt 610-999 an Ezrin/radixin/moesin family (ERM) region, with "a" and "c" allelic variation possible at nts 979, 1080, and 1445, and "a" and "g" possible at nt 1362, and "t" and "c" possible at nts 1996 and 2642.

NCBI # S77910 (SEQ ID NO 164) relates to H4=gene frequently rearranged with the ret proto-oncogene {promoter} [human, Genomic, 447 nt]. Nt 442-447 are said to correspond to the coding sequence, "MA".

NCBI # S72869 (SEQ ID NOs 165 and 166) relate to H4(D10S170)=putative cytoskeletal protein [human, thyroid, mRNA, 3011 nt]. Nt 37-1794 are said to correspond to coding sequence.

NCBI # X65617 (SEQ ID NO 167) relates to a human ret proto-oncogene DNA. Nt 1-54 are said to replace sequences from the H4 gene, nt 55-787 are said to correspond to an intron between the transmembrane and tyrosine kinase domain, and nt 788-808 said to correspond to an exon coding for a tyrosine kinase domain.

### t(12;22)(q13;q12)

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # NM\_005171 (SEQ ID NOs 168 and 169) relate to a human activating transcription factor 1 (ATF1), mRNA. Nt 157-252 are said to correspond to a pKID domain and nt 631-795 are said to correspond to a bZIP transcription factor region.

NCBI # AF047022 (SEQ ID NOs 170 and 171) relate to a human RNA binding protein-activating transcription factor-1 fusion protein (EWS-ATF1) mRNA, partial cds. Nt 1-65 are said to correspond to chromosome 22 and nt 66-353 to chromosome 12, with nt 66^67 said to represent the fusion junction between the EWS and ATF1genes.

## t(12; 16(q13; p11)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # AJ301614 (SEQ ID NO 172) relates to a human t(12;16)(q13;p11) translocation breakpoint (CHOP/FUS chimaeric genomic DNA). Nt 1-225 are said to correspond to the CHOP gene (chromosome 12) and nt 226-500 to the FUS gene (chromosome 16).

NCBI # AJ301613 (SEQ ID NO 173) relates to a human t(12;16)(q13;p11) translocation breakpoint (FUS/CHOP chimaeric genomic DNA). Nt 1-317 are said to correspond to the FUS gene (chromosome 16) and nt 318-521 to the CHOPgene (chromosome 12).

NCBI # AJ301612 (SEQ ID NOs 174 and 175) relate human partial mRNA for FUS/CHOP chimaeric fusion protein (type 9 transcript variant). Nt 1-118 are said to originate from chromosome 16 and nt 119-225 are said to originate from chromosome 12.

NCBI # AJ301611 (SEQ ID NOs 176 and 177) relate to a human partial mRNA for FUS/CHOP chimaeric fusion protein (type 8 transcript variant). Nt 1-128 are said to originate from chromosome 16 and nt 129-235 are said to originate from chromosome 12.

NCBI # NM\_004960 (SEQ ID NOs 178 and 179) relate to a human fusion protein derived from t(12;16) malignant liposarcoma (FUS), mRNA. Nt 79-1659 are said to denote the coding sequence. Allelic variation is stated to be possible at nts 225 (a/c), 369 (c/t), and 1586 (a/g). Nt 937-1173 are said to denote an RNA recognition motif

(RRM), and nt 1354-1425 are said to denote a zinc finger domain in a Ran binding proteins (zf-Ranbp).

NCBI # S75762 (SEQ ID NOs 180 and 181) relate to a FUS...CHOP [human, myxoid liposarcoma specimens, mRNA Partial Mutant, 3 genes, 652 nt]. Nucleotides 1-272 are said to derive from FUS.

NCBI #X71427 (SEQ ID NOs 182 and 183) relate to a human mRNA for FUS-CHOP protein fusion. Nucleotides 70-1458 are said to denote the fusion coding sequence.

NCBI # X71428 (SEQ ID NOs 184 and 185) relate to a human mRNA for FUS gycline rich protein. Nucleotides 73-1650 are said to denote the coding sequence.

NCBI#Y10004 (SEQ ID NO 186) relates to a human DNA fragment containing fusion point of FUS gene and CHOP gene, translocation t(12;16)(q13;p11. The sequence is said to contain 5'-FUS intron 7 sequence and intron 1 3' sequence from CHOP.

NCBI # Y10003 (SEQ ID NO 187) relates to a human DNA fragment containing fusion point of FUS gene and CHOP gene, translocation t(12;16)(q13;p11. The sequence is said to contain 5'-FUS intron 7 sequence and intron 1 3' sequence from CHOP.

NCBI # Y10002 (SEQ ID NO 188) relates to a human DNA fragment containing fusion point of FUS gene and CHOP gene, translocation t(12;16)(q13;p11). The sequence is said to contain 5'-FUS intron 7 sequence and intron 1 3' sequence from CHOP.

NCBI # S75763 (SEQ ID NOs 189 and 190) relate to a FUS...CHOP [human, myxoid liposarcoma specimens, mRNA Partial Mutant, 3 genes, 377 nt]. Nt 1-272 are said to derive from FUS and nt 273-377 from CHOP.

### t(2; 13)(q35;q14)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # U02308 (SEQ ID NOs 191 and 192) relate a human PAX-3-FKHR gene fusion mRNA, partial cds. Nt 1-2070 are said to be coding sequence.

### t(x; 18)(p11.2; q11.2)

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This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S79894 (SEQ ID NOs 193 and 194) relate to a SYT...SSX {translocation breakpoint} [human, synovial sarcoma patient, tumor, mRNA Mutant, 3 genes, 165 nt].

Nt 1-18 are said to derive from SYT and nt 22-165 from SSX.

NCBI # X86175 (SEQ ID NOs 195 and 196) relate to a human mRNA for SSX2 protein. Nt 92-658 are said to be coding sequence.

The following chromosomal aberrations are not discussed in Figure 1 and will now be discussed in more detail:

# t(12:21)(p13:q32)

The TEL (ETV6)-AML1 (CBFA2) gene fusion is the most common reciprocal chromosomal rearrangement in childhood cancer, occurring in approximately 25% of the most predominant subtype of leukemia- common acute lymphoblastic leukemia. Ford et al., Proc. Natl. Acad. Sci. U.S.A. 95 (8), 4584-4588 (1998), reported characterization of the translocation event responsible for one TEL-AML1 genomic sequence in a pair of monozygotic twins diagnosed at ages 3 years, 6 months and 4 years, 10 months with common acute lymphoblastic leukemia. The twins shared an identical rearranged IgH allele. These data have implications for the etiology and natural history of childhood leukemia.

Other articles of interest on this subject include: Wiemels et al., *Protracted and variable latency of acute lymphoblastic leukemia after TEL-AML1 gene fusion in utero*, Blood. 1999 Aug 1;94(3):1057-62; Rubnitz et al., *The role of TEL fusion genes in pediatric leukemias*, Leukemia, 1999 Jan;13(1):6-13. Review; Romana et al., *The t(12;21) of acute lymphoblastic leukemia results in a tel-AML1 gene fusion*, Blood. 1995 Jun 15;85(12):3662-70; Seeger et al., *TEL-AML1 fusion in relapsed childhood acute lymphoblastic leukemia*, Blood. 1999 94(1):374-6; Bayar et al., *Monozygotic twins with congenital acute lymphoblastic leukemia (ALL) and t(4;11)(q21;q23)*, Cancer Genet Cytogenet. 1996 Jul 15;89(2):177-80; Kobayashi et al., *Detection of the Der (21)t(12;21)* 

chromosome forming the TEL-AML1 fusion gene in childhood acute lymphoblastic leukemia, Leuk Lymphoma. 1997 Dec;28(1-2):43-50; and Shurtleff et al., TEL/AML1 fusion resulting from a cryptic t(12;21) is the most common genetic lesion in pediatric ALL and defines a subgroup of patients with an excellent prognosis, Leukemia, 1995 (12):1985-9.

NCBI# AF044317 (SEQ ID NO 197) relates to a human TEL/AML1 fusion gene, partial sequence. This was derived from an ALL infant. Nts 1-407 are said to derive from TEL and nts 408-548 from AML-1.

NCBI # AF231770 (SEQ ID NO 198) relates to a human ETV6/AML1 translocation breakpoint region.

#### t(9:12)(q34; p13)

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In human leukemia, activation of the ABL proto-oncogene locus on chromosome 9 most commonly occurs as a result of its fusion to the BCR locus on chromosome. Papadopoulos et al., Cancer Res. 55 (1), 34-38 (1995), reported a t(9;12) event—a chimeric ABL protein displaying an elevated tyrosine kinase activity fused to a TEL protein from chromosome 12. Like BCR, TEL is fused in-frame with ABL and produces a fusion protein with an elevated tyrosine kinase activity when assayed in an immune complex. The amino-terminal sequences of TEL encodes a helix-loop-helix motif which may mediate dimerization. 43: See also Okuda et al., Oncogene. 1996 Sep 19;13(6):1147-52.

NCBI # Z36279 (SEQ ID NO 199) relates to a human (9TX) breakpoint position DNA for the tel-abl fusion identified by Papadopoulos et al. The translocation breakpoint is said to reside between nt 567 and 568.

#### del(12p)

Revy et al., Cell 102:565-575 (2000), reported hyper IgM immunodeficiencies associated with deletions of 19 and 9 bases at cDNA positions 21 and 175 respectively of the activation-induced cytidine deaminase (AID) gene. The former results in a 6 amino acid deletions and a phe15 to ter premature nonsense codon. The latter results in a 3-amino acid deletion and leu59-to –phe substitution.

NCBI # AB040430 (SEQ ID NOs 200 and 201) relate to a human AID gene for activation-induced cytidine deaminase, complete cds.

NCBI # AB040431 (SEQ ID NO 202 and 203) relate to a human AID mRNA for activation-induced cytidine deaminase, complete cds. Nt 77-673 is said to be coding sequence.

NCBI # NM\_020661 (SEQ ID NOs 204 and 205) relate to a human activation-induced cytidine deaminase (AICDA), mRNA. Nt 77-673 is said to be coding sequence. Allelic variation (a/g) is said to occur at nt 541.

## t(15;17)(q22;q12)

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de The et al., Cell 1991 Aug 23;66(4):675-84, reported a PML-RAR alpha fusion mRNA generated by a t(15;17) translocation associated with acute promyelocytic leukemia (APL). The gene product contained a novel zinc finger motif common to several DNA-binding proteins and the mRNA encoded a predicted 106 kd chimeric protein containing most of the PML sequences fused to a large part of RAR alpha, including its DNA- and hormone-binding domains. In transient expression assays, the hybrid protein exhibited altered transactivating properties if compared with the wild-type RAR alpha progenitor. Identical PML-RAR alpha fusion points were found in several patients, suggesting that in APL the t(15;17) translocation generates an RAR mutant that could contribute to leukemogenesis through interference with promyelocytic differentiation.

NCBI# S50916 (SEQ ID NOs 206 and 207) relate to a PML-RAR fusion gene {fusion transcript} [human, mRNA Partial, 1284 nt]. Nt 1-1251 is said to be coding sequence.

NCBI # M73779 (SEQ ID NOs 208and 209) relate to a human PML-RAR protein (PML-RAR) mRNA, complete cds. Nt 67-2460 is said to be coding sequence.

NCBI # AJ417079 (SEQ ID NOs 210 and 211) relate to a human partial mRNA for PML/RARA fusion protein (PML/RARA gene). Nt 1-109 are said to derive from exon 6 of PML and nts 110-172 and 173-296 are said to derive from intron 2 and exon 3 of RARA.

### t(11;17)(q23;q12)

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Chen et al., EMBO J., 12 (3), 1161-1167 (1993), reported a fusion between a novel Kruppel-like zinc finger gene and the retinoic acid receptor-alpha locus due to a variant t(11;17) translocation associated with acute promyelocytic leukaemia (APL). Chen et al identified mRNAs containing the coding sequences of the new gene, fused in-frame either upstream of the RAR alpha B region or downstream from the unique A1 and A2 regions of the two major RAR alpha isoforms. The new gene, which Chen et al. termed PLZF (for promyelocytic leukaemia zinc finger), encodes a potential transcription factor containing nine zinc finger motifs related to the Drosophila gap gene Kruppel and is expressed as at least two isoforms which differ in the sequences encoding the N-terminal region of the protein. Within the haematopoietic system the PLZF mRNAs are detected in the bone marrow, early myeloid cell lines and peripheral blood mononuclear cells, but not in lymphoid cell lines or tissues. In addition, the PLZF mRNA levels were down-regulated in NB-4 and HL-60 promyelocytic cell lines in response to retinoic acid-induced granulocytic differentiation and were very low in mature granulocytes, suggesting an important role for PLZF as well as retinoic acid and its receptors in myeloid maturation.

NCBI # NM\_006006 (SEQ ID NOs 212 and 213) relate to a human zinc finger protein 145 (Kruppel-like, expressed in promyelocytic leukemia) (ZNF145), mRNA. Nt 76-2097 are said to be coding sequence.

NCBI # Z19002 (SEQ ID NOs 214 and 215) relate to a human PLZF gene encoding kruppel-like zinc finger protein. Nt 76-2097 are said to be coding sequence.

### t(16:16)(p13;q22) and inv(16)

Springall et al., Leukemia 12 (12), 2034-2035 (1998), identified a novel CBFB-MYH11 fusion transcript in a patientwith AML and attributed it to an inversion/translocation of chromosome 16. See also, Krauter et al., Genes Chromosomes Cancer. 2001 Apr;30(4):342-8, Detection and quantification of CBFB/MYH11 fusion transcripts in patients with inv(16)-positive acute myeloblastic leukemia by real-time RT-PCR.; Martinelli et al., Haematologica. 2000 May;85(5):552-5, Long-term disease-free acute myeloblastic leukemia with inv(16) is associated with PCR undetectable CBFbeta/MYH11 transcript; and Dierlamm et al., Genes Chromosomes Cancer. 1998

Jun;22(2):87-94. Review, FISH identifies inv(16)(p13q22) masked by translocations in three cases of acute myeloid leukemia.

NCBI # AF202996 (SEQ ID NOs 216 and 217) relate to a human core binding factor beta-smooth muscle myosin heavy chain fusion protein (CBFB-MYH11) mRNA, partial cds. Nt 1-46 are said to originate from 16q22 and nt 47-89 are are said to originate from 16p13. Nt 50 is said to be a "t" in some reports.

NCBI # AF251768 (SEQ ID NOs 218 and 219) relate to human PCBFB/MYH11E chimeric fusion protein (CBFB/MYH11) mRNA, partial cds. Nt 1-42 are said to derive from exon 5 of CBFB and nts 42-78 from exon 7 of MYH11.

NCBI # AF249898 (SEQ ID NOs 220 and 221) relate to a human PCBFbeta/MYH11A chimeric fusion protein (CBFbeta/MYH11A) mRNA, partial cds. Nt 1-42 are said to derive from exon 5 of CBFB and nts 42-78 from exon 12 of MYH11.

NCBI # AF249897 (SEQ ID NOs 222 and 223) relate to a human s PCBFb-MYH11d chimeric fusion protein (CBFB/MYH11D) mRNA, partial cds.

NCBI # AF390860 (SEQ ID NO 224) relates to a human UPN2 CBFB/MYH11 translocation breakpoint region sequence.

NCBI # AF390859 (SEQ ID NO 225) relates to a human isolate UPN1 CBFB/MYH11 translocation breakpoint region sequence.

## t(9;11)(p22;q23)

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Tkachuk et al., Cell 71: 691-700, (1992), showed that the gene involved in recurring 11q23 leukemogenic translocations codes for an unusually large protein that is a homolog of Drosophila 'trithorax' and is involved in homeotic gene regulation (MLL; aka ALL1). In studies of a t(11;19) translocation, they identified a chimeric protein containing the amino-terminal 'AT-hook' motifs of the MLL gene on chromosome 11 fused to a previously undescribed protein from chromosome 19. The nucleotide sequence determinations demonstrated an open reading frame that coded for a predicted 62-kD protein, which Tkachuk et al. named ENL.

Nakamura et al., Proc. Nat. Acad. Sci. 90: 4631-4635, (1993), showed that the gene on chromosome 19 that is fused to the MLL gene in patients with leukemia and translocation t(11;19)(q23;p13) shows high sequence homology to the genes on chromosome 4 and chromosome 9 that are fused with the ALL1 gene in patients with translocation t(4;11)(q21;q23) and t(9;11)(p22;q23), respectively. The 3 protein gene products contained nuclear targeting sequences as well as serine-rich and proline-rich regions. The results suggested that the different proteins fused to ALL1 polypeptides. These leukemias provide similar functional domains.

Negrini et al., Cancer Res 1993 Oct 1;53(19):4489-92, reported potential topoisomerase II DNA-binding sites at the breakpoints of a t(9;11) chromosome translocation in acute myeloid leukemia. The event examined was a t(9;11)(p22;q23) chromosome translocation and the breakpoints on the two chromosomes occurred within introns of the involved genes: AF-9 on chromosome 9, and ALL-1 on chromosome 11. Sequence analysis identified heptamers flanking the breakpoints on both chromosomes 9 and 11, suggesting that the V-D-J recombinase was involved in the translocation. See also Cimino et al., Cancer Res. 1991 Dec 15;51(24):6712-4, Cloning of ALL-1, the locus involved in leukemias with the t(4;11)(q21;q23), t(9;11)(p22;q23), and t(11;19)(q23;p13) chromosome translocations.

Poirel et al., Blood 87 (6), 2496-2505 (1996), reported an MLL-AF9=fusion gene {fusion site} [human, peripheral blood, acute myeloid leukemia FAB type M1 patient UPN 427, mRNA Partial, 60 nt]; NCBI # S82034 (SEQ ID NO 226), and indicated the breakpoint to be at nucleotide 29.

### t(1;22)(p13;q13)

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Nakamura et al., Proc Natl Acad Sci U S A 1993 May 15;90(10):4631-5,

correlated aberrations on chromosomes 4, 9, and 19 involved in 11q23 abnormalities in acute leukemia with shared sequence homology and/or common motifs, including fusions of the ENL gene with ALL-1 in (11:19) translocations. ENL proteins contain nuclear targeting sequences as well as serine-rich and proline-rich regions. Stretches abundant in basic amino acids are also present.

NCBI # AF364037 (SEQ ID NOs 227 and 228) relate to a human megakaryoblastic leukemia-1 protein/RNA-binding motif protein 15s + ae fusion protein (MKL1/RBM15 fusion) mRNA, complete cds. Ma et al., Nat. Genet. 28 (3), 220-221 (2001) identified this with an acute megakaryoblastic leukemia patient. Nt 144-221 are said to be coding sequence, with nts 1-150 deriving from chromosome 22 and nts 151-300 deriving from chromosome 1.

### t(3;3)(q21;q26) or inv(3)(q21q26)

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Ogawa et al., Oncogene 1996 Jul 4;13(1):183-91 showed that overexpression of the Evi-1 gene appears to be a consistent feature of the 3q21q26 syndrome, an association of myeloid leukemias/myelodysplastic syndrome with a specific chromosomal aberration involving both 3q21 and 3q26, such as t(3;3)(q21;q26) or inv(3)(q21q26). The rearrangement in 3q26 has been reported to occur near the Evi-1 locus, implicating that it is the critical gene deregulated in the 3q21q26 syndrome. Ogawa identified a structural abnormality of Evi-1 protein in a case with the 3q21q26 syndrome. That case carried the typical inv(3)(q21q26), in which the 3q26 breakpoint is located within an intron of the Evi-1 gene, and resulted in overexpression of a normally unexpressed, aberrant form of Evi-1 protein, in which the C-terminal 44 amino acids of wild-type Evi-1 protein were truncated and replaced by five amino acids. The truncated Evi-1 protein was shown to increase AP1 activity when expressed in NIH3T3 cells as its wild-type counterpart. The origin of this peculiar type of rearrangement of the Evi-1 gene was shown not to be an artifact during establishment of the cell line, but rather an event that occurred in the primary leukemic cells, and consistent with 3q21q26 syndrome.

NCBI # S82592 (SEQ ID NOs 229 and 230) relate to an Evi-1=Evi-1 protein {3' region, deletion region} [human, megakaryoblastoid cell line MOLM-1, chronic myelocytic leukemia patient, mRNA Partial Mutant, 916 nt]. Nt 1-132 are said to represent a partial coding sequence.

# t(3;5)(q25;q34)

Yoneda-Kato et al., Oncogene 12: 265-275 (1996), showed that t(3;5)(q25.1;q34) of myelodysplastic syndrome and acute myeloid leukemia produces a novel fusion gene, NPM-MLF1, which results from an in-frame fusion between the 5-prime coding region of

the nucleophosmin gene on chromosome 5 and a gene on chromosome 3, designated MLF1 (myeloid leukemia factor-1). The translocation was identified in 3 t(3;5)-positive cases of AML. Expression of the mRNA was widespread but highest in testis, ovary, skeletal muscle, heart, kidney and colon. Antibodies to MLF1 detected a 31-kD protein in K562 and HEL erythroleukemia cell lines

NCBI # L49054 (SEQ ID NOs 231 and 232) relate to a t(3;5)(q25.1;p34) fusion gene NPM-MLF1 mRNA, complete cds. Nt 109-915 are said to be coding sequence.

NCBI # BC007045 (SEQ ID NOs 233 and 234) relate to a human myeloid leukemia factor 1, clone MGC:12449, mRNA, complete cds. Nt 107-913 are said to be coding sequence.

NCBI # L49054 (SEQ ID NOs 235 and 236) relate to a human t(3;5)(q25.1;p34) fusion gene NPM-MLF1 mRNA, complete cds. Nt 109-915 are said to be coding sequence.

### t(7;11)(p15;p15)

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Borrow et al., Nat. Genet. 1996 Feb;12(2):159-67, reported a t(7;11)(p15;p15) translocation in acute myeloid leukaemia that fused the genes for nucleoporin NUP98 and class I homeoprotein HOXA9.

NCBI # U41814 (SEQ ID NOs 237 and 238) relate to human NUP98-HOXA9 fusion protein mRNA, partial cds. Nt 46^47 are said to represent a NUP98-HOXA9 inframe junction and nt 138^139 are said to be an alternative splice site within HOXA9

NCBI # NM\_002142 (SEQ ID NOs 239 and 240) relate to a human homeo box A9 (HOXA9), mRNA. Nts 67 and 213 are said to have allelic variation possible (c/g), and nt 397-567 and 397-576 are said to respectively represent a homeobox domain and a homeodomain (HOX region).

NCBI # U81511 (SEQ ID NOs 241, 242, and 243) relate to a human HOXA-9A and HOXA-9B (HOXA-9) gene, alternatively spliced, complete cds. Nts 145-502, 4327-4894, and 5893-6131 are said to be exon (coding) sequences, with introns present at 503-5892 and 4895-5892. Alternative splicing events are said to account for the overlap.

## t(8;16)(p11;p13)

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Panagopoulos et al., Genes Chromosomes Cancer. 2000 Aug;28(4):415-24, used RT-PCR analysis to identify MOZ-CBP and CBP-MOZ chimeric transcripts in acute myeloid leukemias with t(8;16)(p11;p13) translocations.

NCBI # AJ251844 (SEQ ID NOs 244 and 245) relate to human partial mRNA for MOZ/CBP chimeric transcript type II. Nt 1-188 are said to derive from chromosome 8 and nts 189-415 from chromosome 16.

NCBI # AJ251845 (SEQ ID NOs 246 and 247) relate to a human partial mRNA for CBP/MOZ chimeric transcript. Nt 1-110 are said to derive from chromosome 16 and nts 111-229 from chromosome 8.

NCBI # AJ251843 (SEQ ID NOs 248 and 249) relate to human partial mRNA for MOZ/CBP chimeric transcript type I. Nt 1-188 are said to derive from chromosome 8 and nts 189-1128 from chromosome 16.

NCBI # U47742 (SEQ ID NOs 250 and 251) relate to human monocytic leukaemia zinc finger protein (MOZ) mRNA, complete cds.

NCBI # U85962 (SEQ ID NOs 252 and 253) relate to a human CREB-binding protein mRNA, complete cds. Nt 814-8147 are said to contain coding sequence and nts 819-1124 are said to encode a nuclear receptor binding domain.

#### t(9;12)(q34;p13)

Papadopoulos et al., Cancer Res. 1995 Jan 1;55(1):34-8, reported activation of ABL by fusion to an ets-related gene, TEL.

NCBI # Z35761 (SEQ ID NOs 254 and 255) relate to a human TEL/ABL fusion protien. Nt 1-463 are said to contain a partial TEL sequence and nt 464-549 are said to contain ABL sequence.

NCBI # Z36279 (SEQ ID NO 256) relates to human (9TX) breakpoint position DNA. The breakpoint position is said to reside at 567..568.

NCBI # Z36278 (SEQ ID NO 257) relates to human (boucher) breakpoint position DNA. The breakpoint position is said to reside at 567..568.

# t(12;22)(p13;q13)

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Buijs et al., Oncogene. 1995 Apr 20;10(8):1511-9, reported that a t(12;22) (p13;q11) event resulted in a myeloproliferative disorders characterized by the fusion of the ETS-like TEL gene on 12p13 to the MN1 gene on 22q11.

NCBI # X85024 (SEQ ID NOs 258 and 259) relate to a human mRNA for TEL-MN1 fusion gene (type II). Nt 22..23 is said to be the fusion site.

NCBI # X85026 (SEQ ID NOs 260 and 261) relate to a human mRNA for a TEL-10 MN1 fusion gene (type I). Nt 22..23 is said to be the fusion site.

NCBI # X85027 (SEQ ID NOs 262 and 263) relate to a human mRNA for a MN1-TEL fusion gene (type II). Nt 22..23 is said to be the fusion site.

NCBI # X85025 (SEQ ID NOs 264 and 265) relate to a human mRNA for a MN1-TEL fusion gene (type I). Nt 22..23 is said to be the fusion site.

#### 15 **del(5q)**

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Jaju et al., Blood 1999 Jul 15;94(2):773-80, reported a recurrent translocation, t(5;11)(q35;p15.5), associated with a del(5q) in childhood acute myeloid leukemia. Partial deletion of the long arm of chromosome 5, del(5q), is the cytogenetic hallmark of the 5q-syndrome, a distinct subtype of myelodysplastic syndrome-refractory anemia (MDS-RA). Deletions of 5q also occur in the full spectrum of other de novo and therapy-related MDS and acute myeloid leukemia (AML) types, most often in association with other chromosome abnormalities. However, the loss of genetic material from 5q is believed to be of primary importance in the pathogenesis of all del(5q) disorders.

Lindgren et al., Am J Hum Genet 1992 May;50(5):988-97, reported phenotypic, cytogenetic, and molecular studies of three patients with constitutional deletions of chromosome 5 in the region of the gene for familial adenomatous polyposis, APC, affiliated with colon cancer and polyps. High-resolution banding studies indicated that some deletions spans the region 5q21-q22..

Other potential deletion aberrations at the 5q locus include but are not limited to deletions at positions 5q13.3, corrsponding to the RASA1 gene encoding the GAP RAS p21 protein activator 1 (GTPase activating protein), aberrancies of which are known to associate with basal cell carcinoma; 5q21, corresponding to the PST gene encoding PST1 Polysialyltransferase; 5q21-q22, corresponding to the APC gene, aberrancies of which correlate with colorectal cancer; 5q31, corresponding to the FACL6 gene encoding ACS2 Fatty-acid-Coenzyme A ligase, a long-chain 6 (long-chain acyl-CoA synthetase 2), aberrancies of which give rise to myelodysplastic syndrome and acute myelogenous leukemia; 5q31, encoding the GRAF GTPase regulator associated with the focal adhesion kinase, aberrancies of which give rise to juvenile myelomonocytic leukemia; 5q31.1, encoding IRF1, a MAR Interferon regulatory factor-1, aberrancies of which give rise to macrocytic anemiam myelodysplastic syndrome (preleukemic), acute myelogenous leukemia, gastric cancer, and nonsmall cell lung cancer; 5q33.2-q33.3, corresponding to CSF1R, FMS Colony-stimulating factor-1 receptor, aberranceis of which have been associated with oncogene FMS (McDonough feline sarcoma), and predisposition to myeloid malignancy; 5q35, encoding NPM1 Nucleophosmin 1 (nucleolar phosphoprotein B23, numatrin), aberrancies of which are known to associate with acute promyelocytic leukemia; 5q35.3, encoding gene FLT4, VEGFR3, encoding PCL fms-related tyrosine kinase-4 (vascular endothelial growth factor receptor, aberrancies of which contribute to hereditary lymphedema.

NCBI # NM\_002387 (SEQ ID NOs 266 and 267) relate to a human gene that is found mutated in colorectal cancers(MCC) mRNA. Nt 221-2710 are said to represent coding sequence. Allelic variation is said to exist at nt 2869 (c/t).

#### del(7q)

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Schwartz et al., Cytogenet. Cell Genet. 51: 152-153 (1991) reported deletion mapping of plasminogen activator inhibitor, type I (PLANH1) and beta-glucuronidase (GUSB) in 7q21-q22. Wedemeyer et al., Genomics 46: 313-315 (1997) reported the proximity of the human HIP1 gene close to the elastin (ELN) locus on 7q11.23. Dridi et al., Am. J. Med. Genet. 87: 134-138 (1999), reported skin elastic fibers in Williams syndrome and Dutly et al., Am. J. Med. Genet. 87: 134-138 (1999), reported unequal interchromosomal rearrangements corresponding to deletions in these genes, and affiliated

with Williams-Beuren syndrome. Naritomi et al., Hum. Genet. 80: 201-202 (1988), reported a microdeletion of the proximal long arm of chromosome 7 affiliated with Zellweger syndrome. Horiike et al., Leukemia. (1999) Aug;13(8):1235-42, reported distinct genetic involvement of the TP53 gene in therapy-related leukemia and myelodysplasia, with chromosomal 7 losses and their possible relationship to replication error phenotype and the development of therapy-related AML/MDS. Wong et al., Cancer Genet Cytogenet. 1995 Jul 1;82(1):70-2, reported biclonal acute monoblastic leukemia associated with del(7q). Particular sites of interest include 7q11.23, encoding PTPN12, PTPG1 Protein tyrosine phosphatase, nonreceptor-type, known to associate with colon cancer; 7q21-q22, encoding PEX1, ZWS1 Peroxisome biogenesis factor-1, associate with Zellweger syndrome-1, neonatal adrenoleukodystrophy and infantile Refsum disease; 7q22-q31.1, encoding SLC26A3, DRA, CLD Solute carrier family 26 (sulfate transporter), member 3, associated with colon cancer; 7q31-q32 SMOH, SMO Smoothened, Drosophila, homolog of 601500, associated with sporadic basal cell carcinoma.

### del(20q)

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A deletion in the long arm of chromosome 20 is a recurring abnormality in malignant myeloid disorders. Its occurrence suggests that the loss of genetic material on 20q provides a proliferative advantage to myeloid cells, possibly through the loss of a tumor-suppressor gene. Roulston et al., Blood 82: 3424-3429 (1993), examined a series of patients with the del(20q) using fluorescence in situ hybridization with unique sequence probes that map along the length of 20q and delineated a segment that is deleted in 95% of all patients they examined (18 of 19). In addition, they showed that the deletions are interstitial rather than terminal. The region of deletion extended from 20q11.2 to 20q12 and was flanked by RPN2 (180490) proximally and D20S17 distally. The SRC (190090) and ADA (102700) genes were found to be located within the commonly deleted segment.

Stoffel et al. (1996) generated a YAC contig map of 20q11.2-q13.1 in a region spanning about 18 Mb and representing about 40% of the physical length of 20q. The map contains the chromosomal regions deleted in MODY1 (125850) and in myeloid leukemia. Using this physical map, they refined the location of a myeloid tumor suppressor-related gene to an 18-cM interval (approximately 13 Mb) between RPN2 and D20S17.

Stoffel et al., Proc. Nat. Acad. Sci. 93: 3937-3941 (1996), correlated the occurrence of del(20q) in a broad spectrum of myeloid disorders, suggesting that the loss of genetic material on 20q could provide a proliferative advantage to myeloid cells, possibly through the loss of a tumor-suppressor gene. Stoffel et al. examined a series of patients with the del(20q) using fluorescence in situ hybridization (FISH) with unique sequence probes that map along the length of 20q, delineated a segment that is deleted in 95% of all patients examined (18 of 19), and showed that the deletions are interstitial rather than terminal. This region of deletion extends from 20q11.2 to q12, and is flanked by the RPN2 (proximal) and D20S17 loci (distal). The SRC and ADA genes are located within the commonly deleted segment.

### t(11q23)

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Shiah et al., Leukemia, (2002) 16(2):196-202, reported clinical and biological implications of partial tandem duplication of the MLL gene in acute myeloid leukemia without chromosomal abnormalities at 11q23. The clinical and biological features of acute myeloid leukemia (AML) with 11q23/MLL translocations are well known, but the characteristics of AML with partial tandem duplication of the MLL gene have not been explored comprehensively. Sheah et al analyzed MLL duplication in 81 AML patients without chromosomal abnormalities at 11q23, using Southern blotting, genomic DNA polymerase chain reaction (PCR), reverse-transcription PCR and complementary DNA sequencing. Nine patients showed partial tandem duplication of the MLL gene, including eight (12%) of the 68 with normal karyotype. Seven patients showed fusion of exon 6/exon 2 (e6/e2), one, combination of differentially spliced transcripts e7/e2 and e6/e2, and the remaining one, combination of e8/e2 and e7/e2. Among the patients with normal karyotype, children aged 1 to 15 showed a trend to higher frequency of MLL duplication than other patients (2/5 or 40% vs 6/62 or 10%, P = 0.102). The patients with tandem duplication of the MLL gene had a significantly higher incidence of CD11b expression on leukemic cells than did those without in the subgroup of patients with normal karyotype (75% vs 28%, P = 0.017). There were no significant differences in the expression of lymphoid antigens or other myeloid antigens between the two groups of patients. In adults, the patients with MLL duplication had a shorter median survival time than those without (4.5 months vs 12 months, P = 0.036). In conclusion, partial tandem duplication of the MLL gene is associated with increased expression of CD11b on leukemic blasts and

implicates poor prognosis in adult AML patients. The higher frequency of MLL duplication in children older than 1 year, than in other age groups, needs to be confirmed by further studies.

Ono et al., Cancer Res. 2002 Jan 15;62(2):333-7, reported that SEPTIN6, a human homologue to mouse Septin6, is fused to MLL in infant acute myeloid leukemia with complex chromosomal abnormalities involving 11q23 and Xq24.

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Borkhardt et al., Genes Chromosomes Cancer. 2001 Sep;32(1):82-8, reported an ins(X;11)(q24;q23) that fuses the MLL and the Septin 6/KIAA0128 gene in an infant with AML-M2.

Luo et al., Mol Cell Biol. 2001 Aug;21(16):5678-87, reported that ELL-associated factor 1 interaction domain is essential for MLL-ELL-induced leukemogenesis.

Kuwada et al., Cancer Res. 2001 Mar 15;61(6):2665-9, reported a t(11;14)(q23;q24) that generates an MLL-human gephyrin fusion gene along with a de facto truncated MLL in acute monoblastic leukemia.

Garcia-Cuellar et al., Oncogene. 2000 Mar 30;19(14):1744-51, reported that ENL, the MLL fusion partner in t(11;19), binds to the c-Abl interactor protein 1 (ABI1) that is fused to MLL in t(10;11)+.

Akao et al., Genes Chromosomes Cancer. 2000 Apr;27(4):412-7, reported an analysis of the rearranged genome and chimeric mRNAs caused by a t(6;11)(q27;q23) chromosome translocation involving MLL in an infant acute monocytic leukemia.

Hayashi et al., Cancer Res. 2000 Feb 15;60(4):1139-45, reported a leukemic cell line, SN-1, associated with a t(11;16)(q23;p13.

So et al., Cancer Genet Cytogenet. 2000 Feb;117(1):24-7, analysed MLL-derived transcripts in an infant acute monocytic leukemia having a complex translocation (1;11;4)(q21;q23;p16).

Kourlas et al., Proc Natl Acad Sci U S A. 2000 Feb 29;97(5):2145-50, identified a gene at 11q23 encoding a guanine nucleotide exchange factor that fuses with MLL in acute myeloid leukemia.

Taki et al., Proc Natl Acad Sci U S A. 1999 Dec 7;96(25):14535-40, reported that AF5q31, an AF4-related gene, is fused to MLL in infant acute lymphoblastic leukemia with an ins(5;11)(q31;q13q23).

Taki et al., Cancer Res. 1999 Sep 1;59(17):4261-5, reported that AF17q25, a putative septin family gene, fuses with the MLL gene in acute myeloid leukemia associatd with a t(11;17)(q23;q25).

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Busson-Le Coniat et al., Leukemia. 1999 Feb;13(2):302-6, reported MLL-AF1q fusion resulting from t(1;11) in an acute leukemia.

Slany et al., Mol Cell Biol. 1998 Jan;18(1):122-9, reported on the oncogenic capacity of HRX-ENL that requires the transcriptional transactivation activity of ENL and the DNA binding motifs of HRX.

Other articles of interest include, Super et al., Genes Chromosomes Cancer. 1997 Oct;20(2):185-95, Identification of complex genomic breakpoint junctions in the t(9;11) MLL-AF9 fusion gene in acute leukemia; Taki et al., Blood. 1997 Jun 1;89(11):3945-50, The t(11;16)(q23;p13) translocation in myelodysplastic syndrome fuses the MLL gene to the CBP gene; Taki Tet al., Fusion of the MLL gene with two different genes, AF-6 and AF-5alpha, by a complex translocation involving chromosomes 5, 6, 8 and 11 in infant leukemia, Oncogene. 1996 Nov 21:13(10):2121-30. Tanabe et al., AF10 is split by MLL and HEAB, a human homolog to a putative Caenorhabditis elegans ATP/GTP-binding protein in an invins(10;11)(p12;q23q12), Blood. 1996 Nov 1;88(9):3535-45; Ma et al., LAF-4 encodes a lymphoid nuclear protein with transactivation potential that is homologous to AF-4, the gene fused to MLL in t(4;11) leukemias, Blood. 1996 Jan 15;87(2):734-45; Prasad et al., Domains with transcriptional regulatory activity within the ALL1 and AF4 proteins involved in acute leukemia, Proc Natl Acad Sci U S A. 1995 Dec 19:92(26):12160-4. Baffa et al., Involvement of the ALL-1 gene in a solid tumor, Proc Natl Acad Sci U S A. 1995 May 23;92(11):4922; Mitani, Cloning of several species of MLL/MEN chimeric cDNAs in myeloid leukemia with t(11;19)(q23;p13.1) translocation, Blood. 1995 Apr 15;85(8):2017-24; Tse et al., A novel gene, AF1q, fused to MLL in t(1:11) (q21;q23), is specifically expressed in leukemic and immature hematopoietic cells, Blood. 1995 Feb 1;85(3):650-6; Chen et al., Acute promyelocytic leukemia: from clinic to molecular biology, Stem Cells. 1995 Jan;13(1):22-31. Review; Rubnitz et al., ENL, the

gene fused with HRX in t(11;19) leukemias, encodes a nuclear protein with transcriptional activation potential in lymphoid and myeloid cells, Blood. 1994 Sep 15;84(6):1747-52; Prasad et al., Leucine-zipper dimerization motif encoded by the AF17 gene fused to ALL-1 (MLL) in acute leukemia, Proc Natl Acad Sci U S A. 1994 Aug 16;91(17):8107-11; Meerabux et al., Molecular cloning of a novel 11q23 breakpoint associated with non-Hodgkin's lymphoma, Oncogene. 1994 Mar;9(3):893-8; Gauwerky et al., Chromosomal translocations in leukaemia, Semin Cancer Biol. 1993 Dec;4(6):333-40. Review; Hunger et al., HRX involvement in de novo and secondary leukemias with diverse chromosome 11q23 abnormalities, Blood. 1993 Jun 15;81(12):3197-203; Morrissey et al., A serine/proline-rich protein is fused to HRX in t(4;11) acute leukemias, Blood. 1993 Mar 1;81(5):1124-31; Tkachuk et al., Involvement of a homolog of Drosophila trithorax by 11q23 chromosomal translocations in acute leukemias, Cell. 1992 Nov 13;71(4):691-700.

### t(5;12)(q31;p13)

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Yagasaki et al. described a fusion of LACS to a TEL/ETV6 gene in an acute myeloblastic leukemia case having a t(5;12) chromosomal translocation. The human mRNA fusion sequence may be found in NCBI # AF102845 (SEQ ID NO 268). Nt 1-40 are said to derive from the TEL gene on chromosome 12 and nt 41-1172 are said to derive from the LACS gene on chromosome 5.

#### t(1;12)(q25;p13)

Cazzaniga et al., Blood 94: 4370-4373 (1999), reported an instance of the tyrosine kinase Abl-related gene ARG fused to ETV6 in an AML-M4Eo patient having a t(1;12)(q25;p13) translocation, and cloned reciprocal chimeric transcripts associated with the event. The ETV6/TEL gene is rearranged in most patients with 12p13 translocations fused to a number of different partners. One of the chimeric proteins consisted of the helix-loop-helix oligomerization domain of ETV6 and the SH2, SH3, and protein tyrosine kinase domains of ABL2. The reciprocal transcript ABL2-ETV6 was also detected in the patient's RNA by RT-PCR, although at a lower expression level.

### t(12;15)(p13;q25)

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Wai et al., Oncogene. 2000 Feb 17;19(7):906-15, reported an ETV6-NTRK3 gene fusion associated with such translocation.

Eguchi et al., Blood. 1999 Feb 15;93(4):1355-63, reported a similar fusion of ETV6 to neurotrophin-3 receptor TRKC in acute myeloid leukemia with t(12;15)(p13;q25).

Knezevich et al., Nat Genet. 1998 Feb;18(2):184-7; reported an ETV6-NTRK3 gene fusion in congenital fibrosarcoma.

NCBI # AF125808 (SEQ ID NOs 269 and 270) relate to a human ETS related protein-neurotrophic receptor tyrosine kinase fusion protein (ETV6-NTRK3 fusion) mRNA, partial cds. Nt 12-64 are said to derive from chromosome 12 and nt 65-980 from chromosome 15.

NCBI # AF041811 (SEQ ID NOs 271 and 272) relate to a human ETS related protein-growth factor receptor tyrosine kinase fusion proteins (ETV6-NTRK3 fusion) mRNA, partial cds. Nt 1-336 are said to derive from chromosome 12 and nt 337-1403 from chromosome 15.

### t(1;12)(q21;p13)

Salomon-Nguyen et al., Proc Natl Acad Sci U S A. (2000) 97(12):6757-62, reported a t(1;12)(q21;p13) translocation observed in a case of acute myeloblastic leukemia (AML-M2). At the protein level, the untranslocated TEL copy and, as a result of the t(1;12) translocation, a fusion protein containing the amino-terminal part of TEL and essentially all of the ARNT gene (126110), were expressed. The TEL/ETV6 gene is located at 12p13 and encodes a member of the ETS family of transcription factors. Translocated ETS leukemia (TEL) is frequently involved in chromosomal translocations in human malignancies, usually resulting in the expression of fusion proteins between the amino-terminal part of TEL and either unrelated transcription factors or protein tyrosine kinases. ARNT (aryl hydrocarbon receptor nuclear translocator) belongs to a subfamily of the "basic region helix-loop-helix" (bHLH) protein that shares an additional region of similarity called the PAS (Per, ARNT, SIM) domain. ARNT is the central partner of

several heterodimeric transcription factors, including those containing the aryl hydrocarbon (dioxin) receptor (AhR) and the hypoxia-inducible factor 1alpha (HIF1alpha). Interference with the activity of AhR or HIF1alpha may contribute to leukemogenesis.

#### 2. Mutant Protein or Cellular Protein Isoforms

The second group of target proteins are mutants or isoforms (e.g. splice variants) of normal cellular proteins (usually the products of tumor suppressor genes) that, due to their mutant nature, exhibit a heightened dependence on HSP90 chaperone functions or else increased senstivity, i.e., instability, due to HSP90 inhibitors. The mutant or isoform proteins either (a) have become overtly oncogenic (a "dominant-positive" (DP) effect), or (b) exert a "dominant-negative" (DN) effect on their normal counterpart, thus preventing the normal protein's tumor suppressor activity, and resulting in a net oncogenic effect. The examples are largely illustrated with respect to human sequences, although the person of ordinary skill will appreciate that homologs in other organisms are likewise included within the purview of the invention.

15 **a. v-src** 

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One such example of a mutant or isoform protein is human v-src (NCBI #s NM 005417; SEQ ID NOs 273 and 274), which counterpart, c-src (NCBI # XM 044659 (SEQ ID NOs 275 and 276), corresponds to the normal cellular gene product. As described above, proteins with a heightened dependence on HSP90 can be identified by their enhanced sensitivity to degradation induced by HSP90 inhibitors, such as the ansamycin antiobiotic geldanamycin. Ansamycins and other HSP90 inhibitors were originally isolated on the basis of their ability to revert v-src transformed fibroblasts (Uehara, Y. et al., 1985, Supra, 76: 672-675) and this reversal was correlated with the functional inactivation of the v-src protein (Uehara, Y. et al., 1986, Mol. Cell. Biol., 6: 2198-2206). This effect was subsequently reported to be caused by the ubiquitin/proteosome-dependent degradation of the transforming v-src protein as a result of inhibition of HSP90 function by geldanamycin (Whitesell, L., et al., 1994, supra). Finally, a recent study compared the rate and potency of degradation of v-src and c-src proteins after treatment of Rous sarcoma virus-transformed 3T3 fibroblasts with the ansamycin geldanamycin. In this study, the oncogenic mutant v-src protein was almost 100% degraded within 6 hours (An, W et al, 2000, supra, see Figure 2), whereas the normal cellular counterpart, c-src, was largely unaffected even after 20 hours of the same treatment (An, W et al, 2000, supra, see Figure 4).

HSP90 inhibitors can selectively induce degradation of a wide range of mutated or otherwise aberrant proteins that cause or exacerbate a disease, and that have an apparent heightened dependence on HSP90.

#### b. RET

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An example of a dominant proto-oncogene encoding a signaling protein that is mutated in certain human cancers giving rise to constitutively active structurally abnormal cellular proteins is the *RET* proto-oncogene (NCBI # P07949; SEQ ID NO 277) in multiple endocrine neoplasia Type 2 (MEN-2). *RET* encodes a receptor tyrosine kinase whose ligand is presently unidentified (Kolibaba, K, *et al*, 1997, *Supra*). The germline mutations found in MEN-2A patients (Cys634-) Arg/Tyr, similar mutations at Cys609, 611, 618 and 620) alter the tertiary structure of the protein resulting in homodimerization and activation of the kinase domain. The commonly observed mutation in MEN-2B, Met918-) Thr, alters the kinase domain structure, causing activation directly. Both of these pathways involve alterations in protein conformation, which again implicates HSP90 and underscores the broad utility of the invention.

c. p53

Another example of a mutant, oncogenic variant group of a normal cellular protein is tumor suppressor antigen p53. The wild-type protein and mRNA sequences for p53 are found in NCBI accession # M14695 (SEQ ID NOs 278 and 279). However, numerous mutations in p53 are known to occur and represent the most common molecular genetic defects found in human cancers (Harris, C et al, 1993, N. Engl. J. Med. 329:1318-1327). A mutant p53 protein was reportedly degraded in cells following treatment with geldanamycin, but wild type p53 exhibited no such, or only minimal, degradation (Blagosklonny, M et al, 1995, Oncogene, 11:933-939). Unlike the situation described above for v-src, most p53 mutations are "loss of function" effects, i.e., the mutation results in the inability of the protein to perform one or more of its normal functions. Thus, in a tumor cell that has an intact p53 allele and a loss of function mutant allele, simply causing the mutant form to be degraded will not change cellular behavior. However, if the mutant protein by some mechanism inhibits the action of its coexpressed normal counterpart inside tumor cells, then degrading it will affect cellular behaviour.

This "dominant-negative" (DN) effect has been shown to occur in cells harboring certain p53 mutants, and by several different mechanisms. For example, a mutant may afford tighter

DNA binding without transactivation (Chene, P, et al, 1999, Int. J. Cancer. 82:17-22). This type of p53 mutant does not exhibit "classical" DN activity unless the mutation confers an increased affinity for DNA, because the mutant stoichiometrically competes with the wild type (WT) protein for binding to DNA. Another example is inhibition of tetramerization by incorporation of one or more mutant p53s into a complex with WT proteins (Deb, D et al, 1999, Int. J. Oncol. 15:413-422, Rollenhagen, C et al, 1998, Int. J. Cancer 78:372-376). Yet a third example concerns "prion-like" activity, in which a mutant protein forces a WT protein into a mutant conformation that then impairs its ability to bind to DNA and/or transactivate p53 target genes (Chene, P, 1998, J. Mol. Biol. 281:205-209)

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Increased stability of mutants relative to WT proteins causes them to accumulate and override normal p53 biology. This is counterintuitive given the fact that p53 has a built-in negative feedback loop on its own transcription (via induction of the mdm-2 protein, which subsequently targets p53 for degradation). If the increased stability of a given mutant were due solely to failure to transactivate mdm-2, then accumulation of the mutant would not occur in the presence of a WT allele (Blagosklonny, M, 2000, *FASEB J.* 14:1901-1907) because this protein would initiate negative feedback mechanisms that would be expected to act on both WT and mutant p53.

On the other hand, an independent mechanism favoring mutant accumulation (e.g. protection by association with HSP90 (Smith, D, et al, 1998, supra; Sepehrnia, B, et al, 1996, J. Biol. Chem. 271:15084-15090) would permit a "recessive" mutant to become in sufficient excess of the transactivating form to result in progressive inhibition of the negative feedback pathways. In this situation, the mutant would have a net DN effect due to progressive accumulation of a stoichiometric antagonist, and selective degradation of that mutant by inhibition of HSP90 activity would be expected to restore normal p53 function. Thus, in most or all cases, a DN phenotype produced by mutant p53 is secondary to the activity of HSP90 and inhibition of HSP90 function with 17-AAG or other HSP90 ATP binding site antagonists would prevent the expression of the DN phenotype and so rescue normal p53 function.

#### i. Dominant negative p53 mutants

A list of exemplary p53 mutations, including examples of structurally-abnormal proteins, dominant-negative proteins, prion-like proteins, and mutants with various combinations of these properties, follows:

Chene *et al*, 1999, *Int. J. Cancer*. 82:17-22; Y236delta (deletion of codon 236) resulted in a conformationally altered & dominant-negative phenotype.

Preuss et al, 2000, Int. J. Cancer 88:162-171); C174Y (Cys→Tyr) (rat) is dominant-negative, non-transactivating. The same mutation at position 176 is predicted to have a similar effect in humans, as the respective homologs have close correlative structural similarities at these positions.

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Srivastava et al, 1993, Oncogene 8:2449-2456); M133T (Met→Thr), G245D (Gly→Asp), and E258K (Glu→Lys) all display conformationally altered, dominant-negative, prion-like displaying activity, in that co-incubation with WT p53 converts it into the mutated conformation.

Deb et al, 1999, Int. J. Oncol. 15:413-422); 1-293delta (deletion of codons 1-293) exhibited dominant negative DNA binding characteristics without transactivating activity.

Frebourg *et al*, 1992, *Proc. Natl. Acad. Sci.* 89:6413-6417; G245C (Gly→Cys), R248W (Arg→Trp), E258K (Glu→Lys), and R282W (Arg→Try) all independently display conformationally altered, dominant-negative activity.

Brachmann *et al*, 1996, *Proc. Natl. Acad. Sci.* 93:4091-4095; novel yeast assay used to identify dominant-negative p53 mutants that have also been found in human tumors, specifically implicating codons 132, 135, 151, 158, 176, 179, 236, 241, 242, 244, 245, 246, 248, 257, 265, 273, 277, 278, 279, 280, and 281. Of particular interest because they exhibited the greatest dominant-negative activity were mutants at codons 241, 242, 244, 245, 246, 248, 277, 278, 279, 280, and 281.

Blagosklonny *et al*, 1995, *Oncogene* 11:933-939); p53s mutated at the following codons exhibited disrupted conformations were dominant negative, and sensitive to geldanamycin: R175H (Arg→His), 194, 213, 223, 248, 274, R280K (Arg→Lys).

Aurelio *et al*, 2000, *Mol. Cell. Biol.* 20:770-778; without identifying conformational status, the following mutants were identified as dominant-negative for transactivation of apoptotic signals (Bax), but not growth arrest signals (p21<sup>WAF</sup>): V143A (Val→Ala), R175H (Arg→His), G245C (Gly→Cys), R248W (Arg→Trp), R273H (Arg→His), K305M (Lys→Met), G325V (Gly→Val).

Marutani *et al*, 1999, *Cancer Res.* 59:4765-4769; yeast-based transdominance assay used to identify dominant-negative mutations at 16 codons: R156H (Arg→His), R175H (Arg→His), P177S (Pro→Ser), H178P (His→Pro), H179R (His→Arg), R181P (Arg→Pro), 238-9delta (deletion of codons 238 & 239), G245S (Gly→Ser), G245D (Gly→Asp), M246R (Met→Arg), R248Q (Arg→Gln), R249S (Arg→Ser), R273H (Arg→His), R273C (Arg→Cys), R273L (Arg→Leu), D281Y (Asp→Tyr).

## ii. Dominant positive p53 mutants

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In addition to dominant-negative mutations, some p53 mutations actually transactivate inappropriate gene expression, contributing to oncogenesis; i.e. a positive tumor promoting effect. See Park et al., 1994, Oncogene 9:1899-1906. This type of mutation is particularly suited to the approach embodied in the present invention because, unlike in the dominant-negative situation, the presence or absence of a normal allele of the tumor suppressor gene is irrelevant to the therapeutic utility of the HSP90 inhibitor. In other words, because the mutant p53 itself contributes to the malignant process, destruction of the mutant protein by inhibition of HSP90 is expected to have direct therapeutic value. A good example is C176Y (Cys-Tyr), as reported by Preuss, U et al, 2000, Int. J. Cancer 88:162-171. This mutant induces rather than represses the cellular fos promoter, resulting in activation of oncogenic signaling pathways. The biology of "dominant-positive" p53 mutants is reviewed in van Oijen et al, 2000, Clin. Cancer Res. 6:2138-2145. Other examples of mutations of p53 that give rise to tumorigenic phenotypes include, but are not limited to, Phe-132, Val-135, Ala-143, His-175, His-179, Trp-248, Ser-249, Leu-273, His-273 and Gly-281. Of particular interest, because these mutant proteins have been shown to be disrupted conformationally, are Ala-143, His-175, His-179 and Gly-281 (van Oijen, M, et al, 2000, supra). Particular subsets of the above list of tumor-promoting mutants have been shown to exert their oncogenic effects via transactivation of one or more of the growth promoting genes bFGF, IGF-1, EGF-R, and c-myc. Alternatively or conjunctively, some gain-of-function mutants, including Ala-143, His-175, Trp-248, Ser-249, His-273, and Gly-281, contribute to tumor resistance to chemotherapeutic drugs by transactivating the MDR gene.

As described above, in the case of this type of mutant, in heterozygous cells, selective degradation of that mutant by inhibition of HSP90 activity will restore normal p53 function. Furthermore, in cases of loss of heterozygosity (LOH), where the tumor has progressed further and the second, normal p53 allele has become mutated or lost, selective degradation of the

mutated protein by inhibition of HSP90 chaperoning will result in a therapeutic effect. In this case the p53 mutant is behaving as an oncoprotein, as in the bcr-abl and v-src examples described above.

#### d. Other tumor suppressor variant proteins

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In addition to p53 itself, additional members of the p53 family of tumor suppressor proteins have also been implicated in human cancer progression. Although p53 itself is a fairly ubiquitous protein, other family members have more restricted tissue distributions. In particular tissues and tumors derived therefrom, closely related non-p53 proteins serve the same role as p53 itself. In these tumors, a truncated variant, termed deltaN, predominates over the full-length form. The truncated and/or deletent isoform is able to compete with the full length form for DNA binding, but does not itself have any transactivating activity. Thus, the deltaN form inhibits the tumor suppressor activity of the full length form, so that if the variant is degraded as a result of inhibition of HSP90 activity, an antitumor effect or drug-sensitizing effect will result. The deltaN isoform will have a heightened dependence on HSP90.

The following three examples concern the specific tumor suppressor proteins p51, p63, and p73. p51 and p63 are each produced from a common 15 exon gene, p73L/p63/p51/p40/KET, and all three proteins exhibit various isoforms, including deltaN isoforms that lack N-terminal transactivation (TA) domains and which are implicated in various carcinomas treatable according to methods of the invention. The many isotypes possible for these gene products are attributable, at least in part, to complex alternative splicing events and, in the case of p63, multiple promoters. For each, it is understood that isoforms may exist and specific isoform expression patterns may vary as between different tissue types, and as between normal versus carcinomic or neoplastic tissues.

#### i. deltaN p51

Osada et al. described the cloning and functional analysis of human p51, which structurally and functionally resembles p53. Nature Med. 4: 839-843 (1998). Two major splicing variant gene products have been detected in normal cells, p51A and p51B. p51A (aka TAp63gamma; NCBI #s AB016072 (SEQ ID NOs 280 and 281) is a 448-amino-acid protein with a molecular weight of 50.9 kDa; and p51B (aka TAp63alpha; AB016073 (SEQ ID NOs 282 and

283) is a 641-amino-acid protein with a molecular weight of 71.9 kDa. Other encoded isoforms have also been observed, including, e.g., those denoted in the following list: p51 delta (NCBI # AF116771 (SEQ ID NOS 284and 285), delNdelta (NCBI # AAF43493 (SEQ ID NOS 286 and 287), delNbeta (NCBI # AAF43492 (SEQ ID NOS. 288 and 289), delNalpha (NCBI # AAF43491 (SEQ ID NOS. 290 and 291), delNgamma (NCBI # AAF43490; SEQ ID NOS 292 and 293), TAp63delta (NCBI # AAF43489; SEQ ID NOS 294 and 295), TAp63beta (NCBI # AAF43488 (SEQ ID NOS 296 and 297), TAp63alpha (NCBI #AAF43487 (SEQ ID NOS 298 and 299), and TAp63gamma (NCBI # AAF43486 (SEQ ID NOS 300 and 301). The TA isoforms contain a transactivation domain (encoded by exon 3') for transactivating p53; the deltaN forms do not. The absence of the TA domain is thought to render those particular isoforms nonfunctional, thereby contributing to carcinoma etiology at least when those isoforms are expressed in abnormally high amounts. Normal expresson patterns of the various isotypes is known to vary as between different tissue types. In lung cancer specimens, for example, multiple deltaN ("TA-less") forms of the p51 protein were found to be overexpressed in 34 of 44 lung cancer specimens analysed (77%). (Tani, M et al, 1999, Neoplasia 1:71-79).

### ii. deltaN p63

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In certain bladder and nasopharyngeal carcinomas, various isoforms of the p53 family member p63 are expressed, and one or more of the deltaN forms, e.g., deltaN p63beta (NCBI #AF075433; SEQ ID NOs 302 and 303), deltaN p63gamma (NCBI #AF075429; SEQ ID NOs 304 and 305), and deltaN p63 alpha (NCBI #AF075431 (SEQ ID NOs 306 and 307) predominate and dominantly inhibit the transactivating activity of the full length TA-containing forms. (Park, B et al, 2000, Cancer Res. 60:3370-3374). The TA-containing isoforms are TA p63 beta (NCBI #AF075432; SEQ ID NOs 308 and 309) and TA p63 alpha (NCBI #AF075430; SEQ ID NOs 310 and 311). In nasopharyngeal carcinoma, the deltaN isoform predominance is even more pronounced (Crook, T et al, 2000, Oncogene 19:3439-3444). The p63 protein is also important in UV-B-induced skin cancer. Overexpression of the deltaN isoform of p63 in transgenic mouse epidermis was found to block apoptosis induced by WT p53 in response to UV-B irradiation (Liefer, K, et al, 2000, Cancer Res. 60:4016-4020). Mutations in the p63 gene have also been reported in epidermal carcinomas. See, e.g., Osada et al, 1998, Nat. Med. 4:839-843 and NCBI #NM003722 (SEQ ID NOs 312 and 313).

#### iii. deltaN p73

The p73 protein is important in ovarian carcinoma – when compared to primary cultures of normal ovarian epithelial cells, 57% of ovarian carcinoma cell lines, 71% of invasive tumors and 92% of borderline tumor tissues were found to express elevated levels of deltaN p73 (Ng, S *et al*, 2000, *Oncogene* 19:1885-1890). Full-length p73 and isoforms thereof are displayed in NCBI # Y11416 (SEQ ID NOs 314, 315, 316, and 317), along with splice and allelic variations, including splice variations responsible for the deltaN isoform.

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Applicants expect that all of the foregoing truncated p53 family members are structurally unstable, dependent on HSP90 and/or exhibit increased sensitivity to HSP90 inhibitors relative to their wild-type counterparts. Applicants further anticipate that other isomeric/aberrant forms of proteins may exhibit similar behavior(s).

The methods of the present invention may be used on mammals, preferably humans, either alone or in combination with other therapies or methods useful for treating a particular cell proliferative disorder or viral infection.

The use of the present invention is facilitated by first identifying whether the cell proliferation disorder or viral infection is accompanied by cells which contain expression of a fusion oncoprotein or a mutated cellular protein with heightened dependence on HSP90 (or a fusion protein or mutant protein that, by one skilled in the art, would be predicted to have heightened dependence on HSP90). Once such disorders are identified, patients suffering from such a disorder can be identified by analysis of their symptoms by procedures well known to medical doctors. Such patients are treated as described herein.

#### 3. Representative assays for diagnosing proliferative disorders

Many different types of methods are known in the art that can be used to diagnose a proliferative disorder characterized by an aberrant protein, *e.g.*, those that involve determining protein concentrations and measuring or predicting the level of proteins within cells, tissues, and fluid samples. Indirect techniques include nucleic acid hybridization and amplification using, *e.g.*, polymerase chain reaction (PCR). These techniques are known to the person of skill and are discussed, *e.g.*, in Sambrook, Fritsch & Maniatis, Molecular Cloning: A Laboratory Manual, Second Edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., Ausubel, *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, NY, 1994. Because the nucleic acid sequence is

known, and because the aberrant proteins have a foundational basis in the nucleic acid sequence, the specific sequences found for aberrant proteins can also be used to generate primers and probes that span the novel junction (in the case of fusion proteins), e.g., using RT-PCR and other procedures. For non-fusion proteins, as well as fusion proteins, stringent hybridization and/or PCR can be used diagnostically.

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Polyclonal or monoclonal antibodies can also be generated based on the specific sequence of the aberrant protein (in the case of fusion proteins, preferably the novel amino acid junction itself) using routine techniques. See Harlow *et al.*, Antibodies: A Laboratory Manual, 2nd Ed; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1988).

Examples of diagnostic methods of that can be used with the invention include those reviewed in Slominski, A et al, 1999, Arch. Pathol. Lab. Med. 123:1246-1259, O'Connor et al, 1999, Leuk. Lymphoma 33:53-63, and Scarpa, A et al, 1997, Leuk. Lymphoma 26 Suppl. 1:77-82. A further list of methods that is intended to be exemplary but not to limit the scope of the invention, follows.

O'Connor *et al*, 1997, *Br. J. Haematol.* 99:597-604 described that the t(15;17)(q22:q21) translocation found in APL produces a PML-RAR fusion protein that can be specifically detected with the 5E10 Mab by fluorescence activated cell sorting (FACS).

Le *et al*, 1998, *Eur. J. Haematol.* 60:217-225 reported that the AML-ETO fusion protein that arises in t(8;21) AML can be identified in tumor cells with ETO-specific polyclonal antibodies using western blotting. The normal ETO protein (70kD) can be distinguished from the AML-ETO fusion protein (94kD) on the basis of their differing mobilities in the gel.

Viswanatha et al, 1998, Blood 91:1882-1890 found that the CBFB-SMMHC fusion protein present in Inv(16)(p13q32) and t(16:16)(p13;q32) AML can be specifically detected with a polyclonal antibody specific for a junctional epitope using FACS of permeabilized cells.

In the case of dominantly-acting mutant proteins, such as mutant RET or gain-of-function mutants of p53, the presence of the specific point mutations known to give rise to the dominant mutant may be identified by the molecular genetic techniques listed above in reference to fusion proteins. Numerous reviews of germline and acquired p53 mutations detected in human cancers have been published (see ,e.g., Hainuit, P, et al, 2000, Adv. Cancer Res. 77:81-137).

In the case of dominant-negative p53 mutations, several other diagnostic criteria may be employed to identify patients susceptible of treatment with the current invention. First, molecular genetic methodologies such as Southern Blotting or PCR can be used to detect the presence of a specific point mutation known to give rise to a dominant-negative version of p53. Similarly, FISH may be employed to detect specific point mutations known to confer conformational changes and/or dominant-negative activity (Villadsen R *et al*, 2000, *Cancer Genet. Cytogenet.* 116:28-34). Other methods include allele-specific PCR (AS-PCR) and chromosome flow cytometry (Villadsen *et al*, *Supra*).

Alternatively, if the mutation in question has not previously been shown to generate a dominant-negative p53 mutant, a cell-based transdominance assay may be used to determine the phenotype (Frebourg, T *et al*, 1992, *Proc. Natl. Acad. Sci.* 89:6413-6417). In this assay, p53-null SAOS-2 cells are co-transfected with WT p53 and the test mutant. The normal p53 protein causes the cells to undergo apoptosis, from which fate they can be rescued by a p53 mutant that has a dominant negative activity. In these cases, further genetic analyses may be performed to confirm the presence of an intact non-mutant allele. In addition, antibodies have been raised that distinguish between p53 proteins with normal versus mutant conformation. These latter p53s have a heightened dependence upon HSP90, and so fall within the scope of the present invention. Specifically, PAb240, from (Oncogene Sciences, Inc.) OSI, is mutant conformation-specific. The corresponding antibody specific for WT is PAb1620, also for OSI (Chene, P, *et al*, 1999, *supra*).

In the case of cell proliferative disorders arising due to unwanted proliferation of non-cancer cells, the level of the fusion protein or mutated cellular protein is compared to that level occurring in the general population (*e.g.*, the average level occurring in the general population of people or animals excluding those people or animals suffering from a cell proliferative disorder). If the unwanted cell proliferation disorder is characterized by an abnormal level of a fusion protein than occurrs in a normal population, or by the presence of a mutated cellular protein, such as p53, then the disorder is a candidate for treatment using the methods described herein. In a preferred example, the mutated protein is p53 and the proliferative disorder is rheumatoid arthritis. In a particularly preferred example, the p53 mutations may include, but are not limited to, N239S (Asn→Ser), C176R (Cys-Arg) and R213\* (Arg→stop) and the mutant forms exert apparent dominant-negative activity over the wild-type protein. (Han, Z *et al*, 1999, *Arthritis Rheum.* 42:1088-1092).

## 4. Preparation and Administration of Pharmaceutical Compositions

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Geldanamycin may be prepared according to U.S. Patent No. 3,595,955 using the subculture of *Streptomyces hygroscopicus* that is on deposit with the U.S. Department of Agriculture, Northern Utilization and Research Division, Agricultural Research, Peoria, Ill., USA, accession number NRRL 3602. It is also available from Sigma/Aldrich Chemical Co., St. Louis, Mo., USA. Numerous derivatives of this compound, including herbimycin A, macbecin, and 17-AAG may be fashioned as specified in U.S. Patent Nos. 4, 261, 989, 5,387,584, and 5,932,566, or according to standard techniques known in the art. Other useful ansamycin derivatives appear in Applicants' co-pending and commonly owned provisonal application entitled, "*Ansamycins Having Improved Pharmacological and Biological Properties*," filed February 8, 2002, Serial Number to be determined, and herein incorporated by reference in its entirety.

Those of ordinary skill in the art are familiar with formulation and administration techniques that can be employed in use of the invention, e.g., as discussed in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, current edition; Pergamon Press; and Remington's Pharmaceutical Sciences (current edition.) Mack Publishing Co., Easton, Pa.

The compounds utilized in the methods of the instant invention may be administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The pharmaceutical compositions used in the methods of the instant invention can contain the active ingredient in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate,

lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, such as microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

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Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents

may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

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The pharmaceutical compositions used in the methods of the instant invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's bloodstream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant

compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS<sup>TM</sup> model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

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The HSP90 inhibitors used in the methods of the present invention may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the inhibitors with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing an HSP90 inhibitor can be used. (As used herein, topical application can include mouth washes and gargles.)

The compounds used in the methods of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The HSP90 inhibitors used in the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the

condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. The instant compounds may also be useful in combination with other inhibitors of parts of the signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation.

The methods of the present invention may also be useful with other agents that inhibit angiogenesis and thereby inhibit the growth and invasiveness of tumor cells, including, but not limited to VEGF receptor inhibitors, angiostatin and endostatin.

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When a HSP90 inhibitor used in the methods of the present invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of a HSP90 inhibitor is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount of each type of inhibitor of between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day. A particular therapeutic dosage that comprises the instant composition includes from about 0.01 mg to about 1000 mg of a HSP90 inhibitor. Preferably, the dosage comprises from about 1 mg to about 1000 mg of a HSP90 inhibitor.

Examples of antineoplastic agents which can be used in combination with the methods of the present invention include, in general, alkylating agents, anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; hormonal/anti-hormonal therapeutic agents and haematopoietic growth factors.

Exemplary classes of antineoplastic agents further include the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the epothilones, discodermolide, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes include, for example, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloromethotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan,

vinblastine, vincristine, leurosidine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estramustine, carboplatin, cyclophosphamide, bleomycin, gemcitibine, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

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The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, preferably from about 1 mg to 300 mg, more preferably 10 mg to 200 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the HSP90 inhibitors used in the methods of the present invention and, if applicable, other chemotherapeutic agents and/or radiation therapy will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the disease being treated. A dosage regimen of the HSP90 inhibitors can be intravenous administration of from 1 mg to 5gm/day, more preferably 10 mg to 2000 mg/day, more preferably still 10 to 1000 mg/day, and most preferably 50 to 600 mg/day, in one or more (preferably two) doses, to block tumor growth.

The chemotherapeutic agent and/or radiation therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent and/or radiation therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the

therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents (i.e., antineoplastic agent or radiation) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

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Also, in general, the HSP90 inhibitor and the chemotherapeutic agent do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the HSP90 inhibitor may be administered orally to generate and maintain good blood levels, while the chemotherapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of HSP90 inhibitor, and chemotherapeutic agent and/or radiation will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

The HSP90 inhibitor, and chemotherapeutic agent and/or radiation may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the proliferative disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (i.e., within a single treatment protocol) with the HSP90 inhibitor.

If the HSP90 inhibitor, and the chemotherapeutic agent and/or radiation are not administered simultaneously or essentially simultaneously, then the optimum order of administration of the HSP90 inhibitor, and the chemotherapeutic agent and/or radiation, may be different for different tumors. Thus, in certain situations the HSP90 inhibitor may be administered first followed by the administration of the chemotherapeutic agent and/or radiation; and in other situations the chemotherapeutic agent and/or radiation may be administration of the HSP90 inhibitor. This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol,

is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient. For example, the chemotherapeutic agent and/or radiation may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of the HSP90 inhibitor followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (therapeutic agent-*i.e.*, HSP90 inhibitor, chemotherapeutic agent or radiation) of the treatment according to the individual patient's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, *e.g.*, CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

#### **EXAMPLES**

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The following examples are illustrative only, and are not intended to be limiting of the invention.

### Example 1:

### Cytotoxic Activity of 17AAG on K562 Versus a Normal Cell Type

Grosveld et al., Mol Cell Biol 6(2):607-16 (1986) showed that the chronic myelocytic cell line K562 produces a chimeric bcr/c-abl transcript, making it a suitable model system to demonstrate the methods of the invention. The cell line is widely available, e.g., from American Type Culture Collection ("ATCC"; Manassas, VA, USA; cat# CCL-243) and can be propogated in a variety of media, e.g., ATCC's Iscove's modified Dulbecco's medium with 4 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate, 90%; fetal bovine serum, 10%; 37C.

### Experimental

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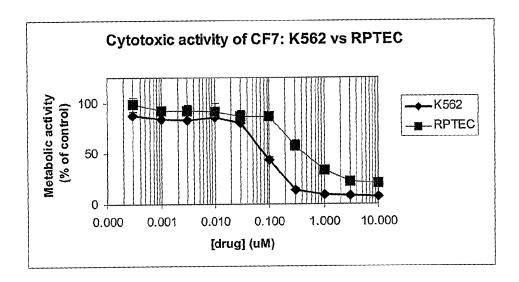
To K562 cells (suspension grown in DMEM media supplemented w/10% Fetal Bovine Serum (FBS) and 1mM HEPES; subcultured biweekly at 100K cells/ml) in a 96 well plate (0.1 ml medium; 2000 cells per well) were added various concentrations of 17-AAG (CF7) and the effects measured over a period of 3-6 days using an MTS assay protocol similar to that offered by Promega Corp (Madison, WI, US; cat# G5421).

The MTS assay is a colorimetric assay for determining the number of viable cells in proliferation, cytotoxicity or chemosensitivity assays. The CellTiter 96® AQueous Assay is composed of solutions of tetrazolium compound (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H- tetrazolium, inner salt; MTS) and an electron coupling reagent (phenazine methosulfate) PMS. MTS is bioreduced by cells into a formazan that is soluble in tissue culture medium. Barltrop et al. (1991) Bioorg. & Med. Chem. Lett. 1, 611. The absorbance of the formazan at 490nm can be measured directly from 96 well assay plates without additional processing. Cory et al. (1991) Cancer Commun. 3, 207; Riss, T.L. and Moravec, R.A. (1992) Mol. Biol. Cell 3 (Suppl.), 184a. The conversion of MTS into the aqueous soluble formazan is accomplished by dehydrogenase enzymes found in metabolically active cells. The quantity of formazan product as measured by the amount of 490nm absorbance is directly proportional to the number of living cells in culture.

Using the MTS assay, cytotoxicity (defined as "growth inhibition" and not necessarily versus renal proximal tubular endothelial cells (normal cells) was determined as shown in the following Tables. "Sem" refers to standard error of the mean, which is calculated as the standard deviation divided by the square root of the sample size; the numbers reflect triplicate replicates. Dilutions of the compounds were prepared in DMSO and straight DMSO was used as a control corresponding to 100% metabolic activity.

j	Metabolic Activity					
Conc (uM)	K562	sem1	RPTEC	sem1		
10.0000	7.89	0.56	20.10	2.64		
3.0000	8.12	1.02	22.01	2.49		
1.0000	9.51	0.59	34.01	0.19		
0.3000	14.40	1.53	58.03	5.09		
0.1000	44.06	2.76	86.46	1.51		
0.0300	80.12	2.29	86.40	5.96		
0.0100	85.94	0.06	91.81	8.22		
0.0030	83.00	2.25	92.73	4.79		

0.0010	83.81	0.73	92.26	2.97
0.0003	88.00	0.40	98.69	7.16



As demonstrated, the fusion protein cancer line K562 is more sensive to the HSP90 inhibitor than is the normal cell line, RPTEC. It is expected that this will hold true for a variety of tumor cell lines versus a variety of normal cell lines.

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In addition to the effects of 17-AAG on K562 versus RPTEC, the effects of a number of other putative HSP90 inhibitors and control compounds were tested side-by-side per the following Table, where "NEC" refers to no effective concentration.

Compound	RPTEC IC <sub>50</sub> (nM)	K562 IC <sub>50</sub> (nM)
CF7	400	70
DMSO	NEC	NEC
208	1000	50
237	4000	100
483	1000	70
481	4000	400

In the table, compound CF7 is the well known 17-AAG and compounds 207, 208, 237, 483, and 481 have the following formulas.

Compound #	Formula
208	MeO H <sub>2</sub> NOCO H <sub>2</sub> a water soluble dimer
237	MeO HO HO OCONH <sub>2</sub> a water soluble dimer
207	MeO HO OME  H <sub>2</sub> NOCO OME  a water soluble dimer
483	MeO HO OME HO OCONH2  a water soluble dimer
481	MeO OH OME  H <sub>2</sub> NOCO OH OME  a water soluble prodrug

A separate study using the well known compound, radicicol, yielded results approximating those obtained for compound 237. Preparation of compounds 207, 208, 237, 483, and 481 is described in the following examples.

# Example 2:

# Preparation of Compound #208

3,3'-diamino-N-methyldipropylamine (1.32g, 9.1mmol) was added dropwise to a solution of Geldanamycin (10g, 17.83mmol) in DMSO (200ml) in a flame-dried flask under N2 and stirred at room temperature. The reaction mixture was diluted with water after 12 hours. A precipitate was formed and filtered to give the crude product. The crude product was chromatographed by silica chromatography (5% CH30H/CH2Cl2) to afford the desired dimer as a purple solid (8.92g, 7.2mmol). Yield: 81%; mp 153oC (dec.); 1H NMR (CDCl3)  $\Box$  0.95 (d, J = 7 Hz, 6H, 2CH3), 1.0 (d, J = 7 Hz, 6H, 2CH3), 1.69 (m, 4 H, 2 CH2), 1.74 (m, 4 H, 2CH2), 1.76 (s, 6 H, 2 CH3), 1.83 (m, 2H, 2CH), 2.0 (s, 6H, 2CH3), 2.3 (s, 3H, N-CH3), 2.36(dd, J = 14Hz, 2H, 2CH), 2.5 (m, 4H, 2CH2), 2.63 (d, 2H, 2CH), 2.75(m, 2H, 2CH), 3.25(s, 6H, 2OCH3), 3.35(s, 6H, 2OCH3), 3.4 (m, 2H, 2CH), 3.50 (m, 4H, 2CH2), 3.68(m, 2H, 2CH), 4.2(Bs, 2H, OH), 4.3( d, J = 10 Hz, 2H, 2CH), 4.8(Bs, 4H, 2NH2), 5.19(s, 2H, 2CH=), 5.82(t, J = 15 Hz, 2H, 2CH=), 5.89(d, J = 10 Hz, 2H, 2CH=), 6.59(t, J = 15 Hz, 2H, 2CH=), 6.92 (d, J = 10 Hz, 2H, 2CH=), 7.13 (t, 2H, 2NH), 7.24(s, 2H, 2CH=), 9.21(s, 2H, 2NH); MS (m/z)1203 (M+H).

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The corresponding HCl salt was prepared by the following method: an HCl solution in EtOH (5 ml, 0.123N) was added to a solution of compound #208 (1 gm as prepared above) in THF (15 ml) and EtOH (50 ml) at room temperature. The reaction mixture was stirred for 10 min. The salt was precipitated, filtered and washed with large amount of EtOH and dried in vacuo.

#### Example 3:

#### Preparation of Compound #207

Compound #207 was prepared by the same method described in example 2 except that 1,4-bis (3-aminopropyl) piperazine was used instead of 3,3'-diamino-N-methyldipropylamine. The pure purple product was obtained after column chromatography (silica gel); yield: 90%; mp 162oC; 1H NMR (CDCl3) □ 0.97 (d, J = 6.6 Hz, 6H, 2CH3), 1.0 (d, J = 6.6 Hz, 6H, 2CH3), 1.73 (m, 4 H, 2 CH2), 1.78 (m, 4 H, 2CH2), 1.80 (s, 6 H, 2 CH3), 1.85 (m, 2H, 2CH), 2.0 (s, 6H, 2CH3), 2.4 (dd, J = 11Hz, 2H, 2CH), 2.55 (m, 8H, 4CH2), 2.67 (d, J = 15 Hz, 2H, 2CH), 2.63 (t, J = 10 Hz, 2H, 2CH), 2.78(t, J = 6.5 Hz, 4H, 2CH2), 3.26(s, 6H, 2OCH3), 3.38(s, 6H, 2OCH3), 3.4 (m, 2H, 2CH), 3.60 (m, 4H, 2CH2), 3.75(m, 2H, 2CH), 4.6( d, J = 10 Hz, 2H, 2CH), 4.65 (Bs, 2H, 2OH), 4.8(Bs, 4H, 2NH2), 5.19(s, 2H, CH), 5.83(t, J = 15 Hz, 2H, 2CH=), 5.89(d, J = 10 Hz, 2H, 2CH=), 6.58(t, J = 15 Hz, 2H, 2CH=), 6.94 (d, J = 10 Hz, 2H, 2CH=), 7.24(s, 2H, 2CH=), 7.60 (m, 2H, 2NH), 9.20(s, 2H, 2NH); MS (m/z) 1258 (M+H); The corresponding HCl salt was prepared by the same procedure as described in example 1.

#### Example 4:

#### Preparation of Compound #237

Compound #237 was prepared by the same method described in example 2 except that 3,3'-diamino-dipropylamine was used instead of 3,3'-diamino-N-methyldipropylamine. The pure purple product was obtained after flash chromatography (silica gel); yield: 93%; mp 165oC; 1H NMR (CDCl3)  $\Box$  0.97 (d, J = 6.6 Hz, 6H, 2CH3), 1.0 (d, J = 6.6 Hz, 6H, 2CH3), 1.72 (m, 4 H, 2 CH2), 1.78 (m, 4 H, 2CH2), 1.80 (s, 6 H, 2 CH3), 1.85 (m, 2H, 2CH), 2.0 (s, 6H, 2CH3), 2.4 (dd, J = 11Hz, 2H, 2CH), 2.67 (d, J = 15 Hz, 2H, 2CH), 2.63 (t, J = 10 Hz, 2H, 2CH), 2.78(t, J = 6.5 Hz, 4H, 2CH2), 3.26(s, 6H, 2OCH3), 3.38(s, 6H, 2OCH3), 3.4 (m, 2H, 2CH), 3.60 (m, 4H, 2CH2), 3.75(m, 2H, 2CH), 4.6( d, J = 10 Hz, 2H, 2CH), 4.65 (Bs, 2H, 2OH), 4.8(Bs, 4H, 2NH2), 5.19(s, 2H, 2CH), 5.83(t, J = 15 Hz, 2H, 2CH=), 5.89(d, J = 10 Hz, 2H, 2CH=), 6.58(t, J = 15 Hz, 2H, 2CH=), 6.94 (d, J = 10 Hz, 2H, 2CH=), 7.17 (m, 2H, 2NH), 7.24(s, 2H, 2CH=), 9.20(s, 2H, 2NH); MS (m/z)1189 (M+H); The corresponding HCl salt was prepared by the same procedure as described in example 1.

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## Example 5:

#### Preparation of Compound #483

Compound #483 was prepared by the same method described in example 2 except that 2,2'-diamino-N-methyldiethyllamine was used instead of 3,3'-diamino-N-methyldipropylamine. The pure purple product was obtained after flash chromatography; yield: 90%; mp 167-169 oC; 1H NMR (CDCl3) □ 0.95 (d, J = 7 Hz, 6H, 2CH3), 1.00 (d, J = 7 Hz, 6H, 2CH3), 1.85 (m, 4 H, 2CH2), 1.75 (s, 6 H, 2 CH3), 1.80 (m, 2H, 2CH), 2.0 (s, 6H, 2CH3), 2.30 (s, 3H, N-CH3), 2.30 (dd, J = 14Hz, 2H, 2CH), 2.5 (m, 4H, 2CH2), 2.63 (d, 2H, 2CH), 2.75(m, 2H, 2CH), 3.25(s, 6H, 2OCH3), 3.35(s, 6H, 2OCH3), 3.4 (m, 2H, 2CH), 3.50 (m, 4H, 2CH2), 3.68(m, 2H, 2CH), 4.2(Bs, 2H, OH), 4.30 (d, J = 10 Hz, 2H, 2CH), 4.8(Bs, 4H, 2NH2), 5.19 (s, 2H, 2CH), 5.82 (t, J = 15 Hz, 2H, 2CH=), 5.90 (d, J = 10 Hz, 2H, 2CH=), 6.59(t, J = 15 Hz, 2H, 2CH=), 6.92 (d, J = 10 Hz, 2H, 2CH=), 7.13 (t, 2H, 2NH), 7.24 (s, 2H, 2CH=), 9.20 (s, 2H, 2NH); MS (m/z)1175 (M+H); ); The corresponding HCl salt was prepared by the same procedure as described in example 1.

#### Example 6:

## Preparation of Compound #481

To 200 mg (0.357 mmol) of geldanamycin in 8 ml of dry THF in a flame-dried flask was added 91.6 mg (0.714 mmol) of N-propyl-1,4-diamino-2-butene drop-wise under nitrogen. The reaction mixture was stirred at room temperature for 4 h at which time TLC analysis indicated the reaction was complete. The solvent was removed by rotary evaporation and the crude material was chromatographed (5% CH3OH/CH2Cl2 to 15% CH3OH/CH2Cl2) to afford the desired compound as a purple solid (150 mg, 0.228 mmol); yield: 64%; mp131oC; 1H NMR (CDCl3) □ 0.97 (m, 9H, 3CH3), 1.52 (m, 2H, CH2), 1.72 (m, 3H, CH + CH2), 1.80 (s, 3 H, CH3), 2.0 (s, 3H, CH3), 2.38 (dd, J = 11Hz, 1H, CH), 2.72 (m, 4H, 2CH, CH2), 3.26(s, 3H, OCH3), 3.38(s, 3H, OCH3), 3.46 (m, H, CH), 3.6 (m, H, CH), 4.18(m, 4H, 2CH2), 4.34( d, J = 10 Hz, 1H, CH), 4.8(Bs, 2H, NH2), 5.19(s, 1H, CH), 5.88(m,4H, 4CH=), 6.38 (m, 1H, NH), 6.61( t, J = 15 Hz, 1H, CH=), 6.94 (d, J = 10 Hz, 1H, CH=), 7.30(s, H, CH=), 9.16(s, H, NH); MS (m/z)658 (M+H). The corresponding HCl salt was prepared by the same procedure as described in example 1.

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Various patents, publications, and formulations are within the levels of ordinary skill in the art to which the invention pertains. All documents including the sequence listing cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually, although none is admitted to be prior art.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, are encompassed within the spirit of the invention, and are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising," "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

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In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group, and exclusions of individual members as appropriate.

#### Claims

#### We claim:

1. A method of treating a patient having a genetically-defined disease characterized by a chromosomal aberration that yields an oncogenic fusion protein, comprising:

providing a cell, tissue, or fluid sample of a patient suspected of having said genetically-defined disease;

identifying one or more characteristics indicative of said disease in or on said cell, tissue, or fluid sample; and

administering to said patient a pharmaceutically effective amount of an HSP90inhibiting compound.

- 2. The method of claim 1, wherein said compound is an ansamycin.
- 3. The method of claim 2, wherein said ansamycin is selected from the group consisting of geldanamycin, 17-AAG, herbimycin A, and macbecin.
- 4. The method of claim 2, wherein said ansamycin is 17-AAG.
- 15 5. The method of claim 1, wherein said compound is a compound that binds into the ATP-binding site of a HSP90.
  - The method of claim 5 wherein said compound is radicicol or an analog thereof.
  - 7. The method of claim 1 wherein said identifying comprises using PCR or LCR to identify a nucleic acid encoding said oncogenic fusion protein.
- 20 8. The method of claim 1 wherein said identifying comprises using an antibody to identify said fusion protein.
  - 9. The method of claim 1 wherein said identifying comprises using a cytochemical technique.
- 10. The method of claim 9 wherein said cytochemical technique employs nucleic acid25 hybridization.

- 11. The method of claim 10 wherein said cytochemical technique is FISH.
- 12. The method of claim 1 wherein said disease is a hematopoietic disorder.
- 13. The method of claim 11 wherein said hematopoietic disorder is selected from the group consisting of a T or B cell lymphoma, CML, APL, ALL, AML, NHL, and CMML.
- 5 14. The method of claim 1 wherein said disease is characterized by a solid tumor.
  - 15. The method of claim 14 wherein said solid tumor is selected from the group consisting of papillary thyroid carcinoma, Ewing's sarcoma, melanoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma.
- 16. The method of claim 1 wherein said fusion protein contains one or more functional domains or portions thereof selected from the group consisting of kinases and DNA binding motifs.
  - 17. The method of claim 12 or 13 wherein said administering employs an ex vivo procedure.
- 15 18. The method of claim 14 wherein said administering is intralesional.
  - 19. The method of claim 1 wherein said administering is parenteral.

- 20. The method of claim 1 wherein said HSP90-inhibiting compound has an IC<sub>50</sub> at least two-fold higher for cells that do not have characteristics indicative of said genetically-defined proliferative disorder relative to those cells that do have such characteristics.
- 21. The method of claim 1 wherein said HSP90-inhibiting compound has an IC<sub>50</sub> at least five-fold higher for cells that do not have characteristics indicative of said genetically-defined proliferative disorder relative to those cells that do have such characteristics.

22. The method of claim 1 wherein said HSP90-inhibiting compound has an  $IC_{50}$  at least ten-fold higher for cells that do not have characteristics indicative of said genetically-defined proliferative disorder relative to those cells that do have such characteristics.

23. The method of claim 1 wherein cells of said patient are monitored *in vitro* for sensitivity prior to administration of said compound to said patient.

- 24. The method of claim 1 wherein said non-random chromosomal aberration is a translocation.
- 25. The method of claim 1 wherein said non-random chromosomal aberration is a inversion.
- 10 26. The method of claim 1 wherein said non-random chromosomal aberration is a deletion.
- 27. The method of claim 1 wherein said non-random chromosomal aberration is selected from the group consisting of inv14 (q11; q32), t(9; 22)(q34; q11), t(1; 19)(q23; p13.3), t(17; 19)(q22; p13), t(15; 17)(q21-q11-22), t(11; 17)(q23; q21.1), t(4; 11)(q21; q23), t(9; 11)(q21; q23), t(11; 19)(q23; p13), t(X; 11)(q13; q23), t(1; 11)(p32; q23), t(6; 11)(q27; q23), t(11; 17)(q23; q21), t(8; 21)(q22; q22), t(3; 21)(q26; q22), 5(16; 21)(p11; q22), t(6; 9)(p23; q34), t(4; 16)(q26; p13), inv(2; 2)(p13; p11.2-14), inv(16)(p13q22), t(5; 12)(q33; p13), t(2; 5)(2p23; q35), t(9:12)(q34:p13), del(12p), t(15;17)(q22;q12), t(11;17)(q23;q12), t(16:16)(p13;q22), inv(16)(p13;q22), t(9;11)(p22;q23), t(1;22)(p13;q13), t(3;3)(q21;q26), inv(3)(q21q26), t(3;5)(q21;q31), t(3;5)(q25;q34), t(7;11)(p15;p15), t(8;16)(p11;p13), t(9;12)(q34;p13), t(12;22)(p13;q13), del(5q), del(7q), del(20q), t(11q23), t(12;21)(p13;q22), t(5;12)(q31;p13), t(1;12)(q25;p13), t(12;15)(p13;q25), t(1;12)(q21;p13), t(12;21)(q13;p32), and t(5;7)(q33;q11.2)).
- The method of claim 1 wherein said non-random chromosomal aberration is a t(9;
   22)(q34; q11) optionally characterized by and comprising a sequence selected from any one of SEQ ID NOs 15-26 or a homolog, isoform, or allelic variation thereof.
  - 29. A method of treating cancerous cells in a heterogeneous population of cells, said heterogeneous population comprising both cancerous and noncancerous, and said

cancerous cells characterized by fusion proteins not found in said noncancerous cells, said method comprising:

administering to said heterogeneous population of cells a pharmaceutically effective amount of an HSP90-inhibiting compound.

- 5 30. The method of claim 29 wherein said compound has an IC<sub>50</sub> that is at least five-fold lower for said cancerous cells than for said noncancerous cells within said heterogeneous population, and wherein said pharmaceutically effective amount administered is about one half or less of the IC<sub>50</sub> of said noncancerous cells.
- 31. The method of claim 29 wherein said compound has an IC<sub>50</sub> that is at least ten-fold lower for said cancerous cells than for said noncancerous cells within said heterogeneous population, and wherein said pharmaceutically effective amount administered is about one half or less of the IC<sub>50</sub> of said noncancerous cells.
  - 32. The method of any of claims 29-31, wherein said compound is an ansamycin.
- 33. The method of claim 32, wherein said ansamycin is selected from the group consisting of geldanamycin, 17-AAG, herbimycin A, and macbecin.
  - 34. The method of claim 33, wherein said ansamycin is 17-AAG.

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- 35. The method of any of claims 29-31 wherein said HSP90-inhibiting compound is a compound that binds the ATP-binding site of a HSP90.
- 36. The method of any of claims 29-31 wherein said cancerous cells are leukemic cells.
  - 37. The method of claim 36 wherein said leukemic cells are selected from the group consisting of a T or B cell lymphoma, CML, APL, ALL, AML, NHL, and CMML.
- 38. The method of any of claims 29-31 wherein said treatment is monitored using one or more techniques selected from the group consisting of PCR, antibody staining, and nucleic acid hybridization, and wherein said techniques are selective for the presence of cancerous cells.

The method of any of claims 29-31 wherein said genetically-defined proliferative disorder is a solid tumor.

40. The method of claim 39 wherein said solid tumor is selected from the group consisting of papillary thyroid carcinoma, Ewing's sarcoma, melanoma, liposarcoma, rhabdomyosarcoma, and synovial sarcoma.

- 41. The method of any of claims 29-31 wherein said fusion protein contains one or more functional domains selected from the group consisting of kinases and DNA binding motifs.
- 42. The method of any of claims 29-31 wherein said administering employs an *ex vivo* procedure.
  - 43. The method of any of claims 29-31 wherein said administering is intralesional.
  - 44. The method of any of claims 29-31 wherein said administering is parenteral.
  - 45. The method of claim 29 wherein said fusion protein arises from a chromosomal translocation.
- 15 46. The method of claim 29 wherein said fusion protein arises from a chromosomal inversion.
  - 47. The method of claim 29 wherein said fusion protein arises from a chromosomal deletion.
- 48. The method of claim 29 wherein said fusion protein is generated from a non-random chromosomal aberration selected from the group consisting of inv14 (q11; q32), t(9; 22)(q34; q11), t(1; 19)(q23; p13.3), t(17; 19)(q22; p13), t(15; 17)(q21-q11-22), t(11; 17)(q23; q21.1), t(4; 11)(q21; q23), t(9; 11)(q21; q23), t(11; 19)(q23; p13), t(X; 11)(q13; q23), t(1; 11)(p32; q23), t(6; 11)(q27; q23), t(11; 17)(q23; q21), t(8; 21)(q22; q22), t(3; 21)(q26; q22), 5(16; 21)(p11; q22), t(6; 9)(p23; q34), t(4; 16)(q26; p13), inv(2; 2)(p13; p11.2-14), inv(16)(p13q22), t(5; 12)(q33; p13), t(2; 5)(2p23; q35), t(9:12)(q34:p13), del(12p), t(15;17)(q22;q12), t(11;17)(q23;q12), t(16:16)(p13;q22), inv(16)(p13;q22), t(9;11)(p22;q23), t(1;22)(p13;q13), t(3;3)(q21;q26), inv(3)(q21q26), t(3;5)(q21;q31), t(3;5)(q25;q34), t(7;11)(p15;p15), t(8;16)(p11;p13), t(9;12)(q34;p13), t(12;22)(p13;q13),

39. The method of any of claims 29-31 wherein said genetically-defined proliferative disorder is a solid tumor.

40. The method of claim 39 wherein said solid tumor is selected from the group consisting of papillary thyroid carcinoma, Ewing's sarcoma, melanoma, liposarcoma, rhabdomyosarcoma, and synovial sarcoma.

- 41. The method of any of claims 29-31 wherein said fusion protein contains one or more functional domains selected from the group consisting of kinases and DNA binding motifs.
- 42. The method of any of claims 29-31 wherein said administering employs an *ex vivo* procedure.
  - 43. The method of any of claims 29-31 wherein said administering is intralesional.
  - 44. The method of any of claims 29-31 wherein said administering is parenteral.
  - 45. The method of claim 29 wherein said fusion protein arises from a chromosomal translocation.
- 15 46. The method of claim 29 wherein said fusion protein arises from a chromosomal inversion.
  - 47. The method of claim 29 wherein said fusion protein arises from a chromosomal deletion.
- 48. The method of claim 29 wherein said fusion protein is generated from a non-random chromosomal aberration selected from the group consisting of inv14 (q11; q32), t(9; 22)(q34; q11), t(1; 19)(q23; p13.3), t(17; 19)(q22; p13), t(15; 17)(q21-q11-22), t(11; 17)(q23; q21.1), t(4; 11)(q21; q23), t(9; 11)(q21; q23), t(11; 19)(q23; p13), t(X; 11)(q13; q23), t(1; 11)(p32; q23), t(6; 11)(q27; q23), t(11; 17)(q23; q21), t(8; 21)(q22; q22), t(3; 21)(q26; q22), 5(16; 21)(p11; q22), t(6; 9)(p23; q34), t(4; 16)(q26; p13), inv(2; 2)(p13; p11.2-14), inv(16)(p13q22), t(5; 12)(q33; p13), t(2; 5)(2p23; q35), t(9:12)(q34:p13), del(12p), t(15;17)(q22;q12), t(11;17)(q23;q12), t(16:16)(p13;q22), inv(16)(p13;q22), t(9;11)(p22;q23), t(1;22)(p13;q13), t(3;3)(q21;q26), inv(3)(q21q26), t(3;5)(q21;q31), t(3;5)(q25;q34), t(7;11)(p15;p15), t(8;16)(p11;p13), t(9;12)(q34;p13), t(12;22)(p13;q13),

del(5q), del(7q), del(20q), t(11q23), t(12;21)(p13;q22), t(5;12)(q31;p13), t(1;12)(q25;p13), t(12;15)(p13;q25), t(1;12)(q21;p13), t(12;21)(q13;p32), and t(5;7)(q33;q11.2)).

- 49. The method of claim 29 wherein said non-random chromosomal aberration is t(9; 22)(q34; q11).
- 5 50. The method of claim 1 or 29 wherein said fusion protein has a heightened dependence on HSP90.
  - 51. The method of claim 20 or 29 wherein said HSP90-inhibiting compound has an  $IC_{50}$  that is lower for cancerous cells than for noncancerous cells.
  - 52. The method of claim 5 or 35 wherein said inhibitor is a synthetic analog of geldanamycin.
- 10 53. A method of treating a patient having a proliferative disease associated with a mutant protein or cellular protein isoform dependent on HSP90, comprising:

providing a cell, tissue, or fluid sample of a patient suspected of having said proliferative disease;

identifying in said cell, tissue, or fluid sample one or more characteristics indicative of said mutant protein or cellular protein isoform; and

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administering to said patient a pharmaceutically effective amount of an HSP90-inhibiting compound.

- 54. The method of claim 53 wherein said mutant protein or cellular protein isoform is selected from the group consisting of src, RET, p53, p51, p63, p73, and homologs and allelic variations thereof.
- 55. The method of claim 53 wherein said mutant protein or cellular protein isoform is a dominant negative mutant.
- 56. The method of claim 53 wherein said mutant protein or cellular protein isoform is a human p53 selected from the group consisting of N239S, C176R, and R213\*, Y236delta, C176Y, M133T, G245D, E258K, 1-293delta, G245C, R248W, E258K, R282W, R175H.

R280K, V143A, R175H, P177S, H178P, H179R, R181P, 238-9delta, G245S, G245D, M246R, R248Q, R249S, R273H, R273C, R273L, and D281Y.

- 57. The method of claim 53 wherein said mutant protein or cellular protein isoform is a dominant positive mutant.
- 5 58. The method of claim 57 wherein said mutant protein or cellular protein isoform is a C176Y mutant.
  - 59. The method of claim 53 wherein said patient is heterozygous for said mutant protein or cellular protein isoform.
- 60. The method of claim 59 wherein said mutant protein or cellular protein isoform is p53 and wherein said proliferative disease is rheumatoid arthritis.
  - 61. The method of claim 53, wherein said compound is an ansamycin.
  - 62. The method of claim 61, wherein said ansamycin is selected from the group consisting of geldanamycin, 17-AAG, herbimycin A, and macbecin.
  - 63. The method of claim 62, wherein said ansamycin is 17-AAG.

- 15 64. The method of claim 53, wherein said inhibitor is a compound that binds into the ATP-binding site of a HSP90.
  - 65. The method of claim 64 wherein said compound is radicical or an analog thereof.
  - 66. The method of claim 53 wherein said identifying comprises using at least one technique selected from the group consisting of nucleic acid hybridization, PCR, LCR, antibody staining, and immunoprecipitation to determine the presence of said mutant protein or cellular protein isoform.
  - 67. The method of claim 53 wherein said administering employs an ex vivo procedure.
  - 68. The method of claim 53 wherein said administering is intralesional.
  - 69. The method of claim 53 wherein said administering is parenteral.

70. The method of claim 53 wherein said HSP90-inhibiting compound has an IC<sub>50</sub> at least two-fold higher for cells that do not have characteristics indicative of said mutant protein or cellular protein isoform relative to those cells that do have such characteristics.

71. The method of claim 53 wherein said HSP90-inhibiting compound has an IC $_{50}$  at least ten-fold higher for cells that do not have characteristics indicative of said mutant protein or cellular protein isoform relative to those cells that do have such characteristics.

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- 72. The method of claim 53 wherein cells of said patient are monitored *in vitro* for sensitivity prior to administration of said compound to said patient.
- 73. A method of selectively treating cells that express a mutant protein or cellular protein isoform that gives rise to a proliferative disorder dependent on HSP90, said method comprising:

providing a population of cells in which at least some of said population express a mutant protein or cellular protein isoform that is differentially dependent on HSP90 for effect and gives rise to a proliferative disorder, and

administering to said population a pharmaceutically effective amount of an HSP90-inhibiting compound.

- 74. The method of claim 73 wherein said compound has an IC<sub>50</sub> that is at least five-fold lower for said cells that express said mutant protein or cellular protein isoform than for those cells that do not, and wherein said pharmaceutically effective amount administered is about one half or less of the IC<sub>50</sub> of cells that do not express said mutant protein or cellular protein isoform.
- 75. The method of claim 73 wherein said compound has an IC<sub>50</sub> that is at least ten-fold lower for said cells that express said mutant protein or cellular protein isoform than for those cells that do not, and wherein said pharmaceutically effective amount administered is about one half or less of the IC<sub>50</sub> of cells that do not express said mutant protein or cellular protein isoform..
- 76. The method according to any of claims 73-75, wherein said compound is an ansamycin.

77. The method of claim 76, wherein said ansamycin is selected from the group consisting of geldanamycin, 17-AAG, herbimycin A, or macbecin.

- 78. The method of claim 77, wherein said ansamycin is 17-AAG.
- 79. The method of any of claims 73-75, wherein said compound is a compound that binds the ATP-binding site of a HSP90.
  - 80. The method of claim 79 wherein said compound is radicical or an analog thereof.
  - 81. The method of any of claims 73-75 wherein said treatment is monitored using one or more techniques selected from the group consisting of PCR, LCR, nucleic acid hybridization, antibody labeling, and immunoprecipitation, and wherein said techniques are selective for the presence of said mutant protein or cellular protein isoform.
  - 82. The method of any of claims 73-75 wherein said administering employs an *ex vivo* procedure.
  - 83. The method of any of claims 73-75 wherein said administering is intralesional.
  - 84. The method of any of claims 73-75 wherein said administering is parenteral.
- 15 85. The method of claim 76 wherein said HSP90-inhibiting compound has an IC<sub>50</sub> that is lower for cells expressing the mutant protein or cellular protein isoform than for cells that do not express said mutant protein or cellular protein isoform.
  - 86. The method of claim 64 or 73 wherein said inhibitor is a synthetic analogue of geldanamycin.
- 20 87. The method of claim 73 wherein said mutant protein or cellular protein isoform is selected from the group consisting of src, RET, p53, p51, p63, p73, and homologs and allelic variations thereof.
  - 88. The method of claim 73 wherein said mutant protein or cellular protein isoform is a dominant negative mutant.

89. The method of claim 88 wherein said mutant protein or cellular protein isoform is a human p53 selected from the group consisting of N239S, C176R, and R213\*, Y236delta, C174Y, M133T, G245D, E258K, 1-293delta, G245C, R248W, E258K, R282W, R175H, R280K, V143A, R175H, P177S, H178P, H179R, R181P, 238-9delta, G245S, G245D, M246R, R248Q, R249S, R273H, R273C, R273L, and D281Y.

- 90. The method of claim 73 wherein said mutant protein or cellular protein isoform is a dominant positive mutant.
- 91. The method of claim 90 wherein said mutant protein or cellular protein isoform is C176Y human p53, or a homolog thereof.
- 10 92. The method of claim 73 wherein said cells that express a mutant protein or cellular protein isoform are heterozygous for said mutant protein or cellular protein isoform.
  - 93. The method of claim 92 wherein said mutant protein or cellular protein isoform is p53 and wherein said proliferative disease is rheumatoid arthritis or a cancer.

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Type of Aberration	Background Literature	Affected Gene(s)	Protein Domain	Fusion Protein	Disease
t(9; 22)(q34; q11)	de Klein, A. et al. Nature 300, 765-767 (1982)	CABL (9q34) BCR (22q11)	tyrosine kinase serine kinase	serine + tyrosine kinase	CML/ALL
inv14 (q11; q32)	Baer, R., Chen, KC., Smith, S. D. & Rabbitts, T. H. Cell 43, 705-713 (1985); Denny, C. T. et al. Nature 320, 549-551 (1986)	TCR-α (14q11) VH-(14q32)	TCR-Cα lg VH	VH-TCR-Cα	T/B-cell lymphoma
t(1; 19)(q23; p13.3)	Kamps, M. P., Murre., C., Sun, XH. & Baltimore, D. Cell 60, 547-555 (1990); Nourse, J. et al. Cell 60, 535-545 (1990)	PBXI (1q23) E2A (19p13.3)	HD AD-b-HLH	AD + HD	pre-B-ALL
t(17; 19)(q22; p13)	Hunger, S. P., Ohyashiki, K. Toyama, K. & Clearly, M. L. Genes Dev. 6, 1608-1620 (1992); Inaba, T. et al. Science 257, 531-534 (1992)	HLF (17q22) E2A (19p13)	bZIP AD-b-HLH	AD + bZIP	pro-B-ALL
t(15; 17)(q21-q11-22)	Giliard, E. F. & Solomon, E. Sem. Cancer Biol. 4, 359-368 (1993)	PML (15Q21) RARA (17q21)	Zinc-finger Retinoic acid receptor- $lpha$	Zinc-finger + RAR DNA and ligand binding	APL
t(11; 17)(q23; q21.1)	Chen, Z. et al. EMBO J. 12, 1161-1167 (1993)	PLZF (11q23) RARA (17q21)	Zinc-finger Retinoic acid receptoro	Zn-finger + RAR DNA and ligand binding	APL
t(4; 11)(q21; q23)	Djabali, M. et al. Nature Genet. 2, 113-118 (1992); Gu, Y. et al. Cell 71, 701-708 (1992)	MLL (11q23) AF4 (4q21)	A-T hook/Zn-finger Ser-Pro rich	A-T hook + (Ser-pro)	ALL/preB-ALL/
t(9; 11)(q21; q23)	Nakamura, T. et al. Proc. natn. Acad. Sci. U.S.A. 90, 4631-4635 (1993); Lida, S. et al. Oncogene 8, 3085-3092 (1993)	MLL (11q23) AF9/MLLT3 (9p22)	A-T hook/Zn-finger Ser-Pro rich	A-T book + (Ser-Pro)	ALL/preB- ALL/ ALL/ ANLL
t(11; 19)(q23; p13)	Tkachuk, D. C., Kohler, S. & Cleary, M. L. Cell 71, 691-700 (1992); Yamamoto, K. et al. Oncogene 8, 2617-2625 (1993)	MLL (11q23) ENL (19p13)	A-T hook/Zn-finger Ser-Pro rich	A-T hook + Ser-Pro	pre-B-ALL/ T-ALL/ ANLL

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	Type of Aberration	Background Literature	Affected Gene(s)	Protein Domain	Fusion Protein	Disease
-	t(X; 11)(q13; q23)	Соттаl, J. et al. Proc. natn. Acad. Sci. U.S.A. 90, 8538-8542 (1993)	MLL (11q23) AFXI (Zq13)	A-T hook/Zn-finger Ser-Pro rich	A-T hook + (Ser-Pro)	T-ALL
<del>-</del>	t(1; 11)(p32; q23)	Bernard, O. A., Mauchauffe, M., Mecucci, C., Van Den Berghe, H. & Berger, R. Oncogene 9, 1039-1045 (1994)	MLL (11q23) AFIP (1p32)	A-T hook/Zn-finger Eps-15 homologue	A-T hook +	ALL
-	t(6; 11)(q27; q23)	Prasac, R. et al. Cancer Res. 53, 5624-5628 (1993)	MLL (11q23) AF6 (6q27)	A-T hook/Zn-finger myosin homologue	A-T hook +	ALL
•	t(11; 17)(q23; q21)	Prasac, R. et al. Proc. natn. Acad. Sci. U.S.A. 91, 8107-8111 (1994)	MLL (11q23) AF17 (17q21)	A-T hook/Zn-finger Cys-rich/leucine zipper	A-T hook + leucine zipper	AML
	t(8; 21)(q22; q22)	Ohki, M. Sem. Cancer Biol. 4, 369-376 (1993)	ΑΜΕ1/CBFα (21q22) ΕΤΟ/MTG8 (8q22)	DNA binding/runt homology Zn-finger	DNA binding + Zn- fingers	AML
-	t(3; 21)(q26; q22)	Mitani, K. et al. EMBO J. 13, 504-510 (1994)	AMLI (21q22) EVI-I (3q26)	DNA binding Zn-finger	DNA binding $+Zn$ -fingers	CML
-	t(3; 21)(q26; q22)	Nucifora, G., Begy, C. R., Erickson, P., Drackin, H. A. & Rowley, J. D. Proc. natn. Acad. Sci. U.S.A. 90, 7784-7788 (1993)	AML I (21q22) EAP (3q26)	DNA binding Sn protein	DNA binding + out-of-frame EAP	Myelo- dyspiasia
•	5(16, 21)(p11; q22)	Shimizu, K. et al. Proc. natn. Acad. Sci. U.S.A. 90, 10280-10284 (1993)	FUS (16p11) ERG (21q22)	Gin-Ser Tyr/Gly- rich/RNA binding Ets-like DNA binding	Gin-Ser-Tyr + DNA binding	Myeloid
<del>-</del>	t(6; 9)(p23; q34)	von Lindern, M. et al. Molec. Cell Biol. 12, 1687-1697 (1992)	DEK (6p23) CAN (9q34)	unkown ZIP	ZIP+	AML
	9; 9?	von Lindern, M., Breems, D., van Baai, S., Acriaansen, H. & Grosveld, G. Genes Chrom. Cancer 5, 227-234 (1992)	SET (9q34) CAN (9p34)	ZIP	ZIP+	AUL
-	t(4; 16)(q26; p13)	Laabi, Y. et al. EMBO J. 11, 3897-3904 (1992)	IL-2 (4q26) BCM (16p13.1)	IL.2 TM domain	IL-2/TM	T-lymphoma

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# FIGURE 1 (Cont'd)

Type of Aberration	Background Literature	Affected Gene(s)	Protein Domain	Fusion Protein	Disease
inv(2; 2)(p13; p11.2-14)	Lu, D. et al. Oncogene 6, 1235-1241 (1991)	REL (2p13) NRG (2p11.2-14)	DNA binding-activator not known	DNA binding +	NHL
inv(16)(p13q22)	Liu, P. et al. Science 261, 1041-1044 (1993)	Myosin MYH11 (16p13) CBF-β (16q22)		DNA binding?	AML
t(5; 12)(q33; p13)	Golub, T. R., Barker, G. F., Lovett, M. & Gilliland, D. G. Cell 77, 307-316 (1994)	PDGF-β (5q33) TEL (12p13)	Receptor kinase Ets-like DNA binding	Kinase + DNA binding	CMML
t(2; 5)(2p23; q35)	Morris, S. W. et al. Science 263, 1281-1284 (1994)	NPM (5q35) ALK (2p23)	Nuclear phosphoprotein Tyrosine kinase	N terminus NPM + kinase	NHL
t(11; 22)(q24; q12)	Delattre, O. et al. Nature 359, 162-165 (1992)	FLII (11q24) EWS (22q12)	Ets-like DNA binding Gin-Ser-Tyr/Gly- rich/RNA binding	Gin-Ser-Tyr + DNA binding	Ewing's sarcoma
inv10(q11.2; q21)	Pierotti, M. A. et al. Proc. natn. Acad. Sci. U.S.A. 89, 1616-1620 (1992)	RET (10q11.2) D10S170 (q21)	tyrosine kinase uncharacterized	Unk + tyrosine kinase	Papillary thyroid
t(12; 22)(q13; q12)	Zucman, J. et al. Nature Genet. 4, 341-345 (1993)	ATFI (12q13) EWS (22q12)	bZIP Gln-Ser-Tyr/Gly- rich/RNA binding	Gin-Ser-Tyr + bZIP	carcinoma a melanoma
t(12; 16)(q13; p11)	Crozat, A., Aman, P., Mandahl, N. & Ron, D. Nature 363, 640-644 (1993); Rabbitts, T. H.; Forster, A., Larson, R. & Nathan, P. Nature Genet. 4, 175-180 (1993)	CHOP (12q13) FUS (16p11)	(DNA binding?)/ZIP Gln-Ser-Tyr/Gly- rich/RNA binding	Gin-Ser-Tyr +(DNA binding?)/ZIP	Liposarcoma
t(2; 13)(q35; q14)	Bern-David, Y., Giddens, E. B., Letwin, K. & Bernstein, A. Genes Dev. 5, 908-918 (1991)	<i>PAX3</i> (2q35) <i>FKHR</i> (13q14)	Paired box/homeodomain Forkhead domain	PB/HD +DNA binding	Rhabdomyosar coma
t(X; 18)(p11.2;q11.2)	Clark, J. et al. Nature Genet. 7, 502-5087 (1994)	SYT (18q11.2) SSX (Xp11.2)	None identified None identified		Synovial sarcoma

#### 1/299

#### SEQUENCE LISTING

<110> CONFORMA THERAPEUTICS CORP. <120> METHODS FOR TREATING GENETICALLY-DEFINED PROLIFERATIVE DISORDERS WITH HSP90 INHIBITORS <130> 031164.0010WO <140> <141> <150> 60/272,751 <151> 2001-03-01 <160> 330 <170> PatentIn Ver. 2.1 <210> 1 <211> 46 <212> PRT <213> Homo sapiens Ile Pro Leu Thr Ile Asn Lys Glu Asp Asp Glu Ser Pro Gly Leu Tyr 1 5 Gly Phe Leu Asn Val Ile Val His Ser Ala Thr Gly Phe Lys Gln Ser Ser Ser Glu Lys Leu Arg Val Leu Gly Tyr Asn His Asn Gly 40 <210> 2 <211> 140 <212> DNA <213> Homo sapiens <400> 2 attccgctga ccatcaataa ggaagatgat gagtctccgg ggctctatgg gtttctgaat 60 gtcatcgtcc actcagccac tggatttaag cagagttcaa gtgaaaagct ccgggtctta 120 ggctataatc acaatgggga 140 <210> 3 <211> 561 <212> DNA <213> Homo sapiens <400> 3 gagcagcaga agaagtgttt cagaagcttc tccctgacat ccgtggagct gcagatgctg 60 accaactcgt gtgtgaaact ccagactgtc cacagcattc cqctqaccat caataaqqaa 120 gatgatgagt ctccggggct ctatgggttt ctgaatgtca tcqtccactc aqccactqqa 180 tttaagcaga gttcaagaag aagccatacg gtgaaccagg tgatgctgag qttatctgga 240 tocaggocat gcagatgaag ccatatttac ctttgtgata ttqqqqqctqa tcttqqaqct 300 gtctggatct gaccagtctc caggttgaaa actcttgcaa ctttcgtttt tggatagtgc 360

#### 2/299

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Val His Ser Ile Pro Leu Thr Ile Asn Lys Glu Asp Asp Glu Ser Pro 165 170 175

Gly Leu Tyr Gly Phe Leu Asn Val Ile Val His Ser Ala Thr Gly Phe 180 185 190

Lys Gln Ser Ser Lys Leu Gln Arg Pro Val Ala Ser Asp Phe Glu Pro 195 200 205

Gln Gly Leu Ser Glu Ala Ala Arg Trp Asn Ser Lys Glu Asn Leu Leu 210 215 220

Ala Gly Pro Ser Glu Asn Asp Pro Asn Leu Phe Val Ala Leu Tyr Asp 225 230 235 240

Phe Val Ala Ser Gly Asp Asn Thr Leu Ser Ile Thr Lys Gly Glu Lys

3/299

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4/299

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5/299

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Tyr Glu Arg Ala Glu Trp Arg Glu Asn Ile Arg Glu Gln Gln Lys Lys
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Ile Val His Ser Ala Thr Gly Phe Lys Gln Ser Ser Lys Ala Leu Gln
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Arg Trp Asn Ser Lys Glu Asn Leu Leu Ala Gly Pro Ser Glu Asn Asp 145 150 150 160

Pro Asn Leu Phe Val Ala Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn 165 170 175

Thr Leu Ser Ile Thr Lys Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn 180 185 190

His Asn Gly Glu Trp Cys Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp 195 200 205

Val Pro Ser Asn Tyr Ile Thr Pro Val Asn Ser Leu Glu Lys His Ser 210 215 220

Trp Tyr His Gly Pro Val Ser Arg Asn Ala Ala Glu Tyr Leu Leu Ser 225 230 235 240

Ser Gly Ile Asn Gly Ser Phe Leu Val Arg Glu Ser Glu Ser Ser Pro 245 250 255

6/299

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Tyr Gly Phe Leu Asn Val Ile Val His Ser Ala Thr Gly Phe Lys Gln

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7/299

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9/299

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10/299

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12/299

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13/299

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14/299

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15/299

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Phe Thr Phe		yr Trp Met 1	His Trp Val	Arg Gln Al	a Pro Gly	
Lys Gly Let 50	u Val Trp V	al Ser Arg 55	Ile Asn Ser	Asp Gly Se	r Ser Thr	
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Ser Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn

16/299

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377

17/299

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18/299

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Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Ser Ile Tyr His Ser Gly
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19/299

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20/299

616 .

201277																
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21/299

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Glu Gln Ser Arg Thr Arg Pro Ile Ser Pro Lys Glu Ile Glu Arg Met 305 310 315 320

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Gln Ser Thr Cys Glu Ala Val Met Ile Leu Arg Ser Arg Phe Leu Asp 340 345 350

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22/299

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25

23/299

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24/299

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		gaaattctgc				
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	Julia	-sygattiti	cagceceerg	ccccagage	acceaatect	3500

## 26/299

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<212> PRT

<213> Homo sapiens

<400> 46

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35 40 45

Ser Ser Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly 50 60

Phe Phe Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg 65 70 75 80

Asp Lys Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr 85 90 95

Cys Arg Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val
100 105 110

Arg Asn Asp Arg Asn Lys Lys Lys Glu Val Pro Lys Pro Glu Cys 115 120 125

Ser Glu Ser Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys 130 135 140

Val Arg Lys Ala His Gln Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly 145 150 155 160

Lys Tyr Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile 165 170 175

Asp Leu Trp Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys 180 185 190

Thr Val Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile 195 200 . 205

Ala Asp Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile 210 215 220

27/299

Leu Arg Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe 225 230 235 Ser Asp Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe 245 250 Gly Pro Leu Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro 265 Leu Glu Met Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys Gly Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met 295 Leu Gln Glu Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro Ser Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr 325 330 Asp Leu Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu 360 Glu Asn Ser Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly 375 Gly Arg Asp Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro 385 390 Ser Leu Ser Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro 405 <210> 47 <211> 1284 <212> DNA <213> Homo sapiens <400> 47 cccaacagca accacgtggc cagtggcgcc ggggaggcag ccattgagac ccagagcagc 60 agttetgaag agatagtgee cageeeteee tegecaceee etetaceeeg catetacaaq 120 ccttgctttg tctgtcagga caagtcctca ggctaccact atggggtcag cgcctgtgag 180 ggctgcaagg gcttcttccg ccgcagcatc cagaagaaca tggtgtacac gtgtcaccgg 240 gacaagaact gcatcatcaa caaggtgacc cggaaccgct gccagtactg ccgactgcag 300 aagtgctttg aagtgggcat gtccaaggag tctgtgagaa acgaccgaaa caagaagaag 360 aaggaggtge ccaagecega gtgetetgag agetacaege tgaegeegga ggtgggggag 420 ctcattgaga aggtgcgcaa agcgcaccag gaaaccttcc ctgccctctg ccagctgggc 480 aaatacacta cgaacaacag ctcagaacaa cgtgtctctc tggacattga cctctgggac 540 aagttcagtg aactctccac caagtgcatc attaagactg tggagttcgc caagcagctg 600 cccggcttca ccacctcac catcgccgac cagatcaccc tcctcaagqc tqcctqcctq 660 gacatcctga tcctgcggat ctgcacgcgg tacacgcccg agcaggacac catgaccttc 720 teggaegge tgaecetgaa eeggaeceag atgeacaaeg etggettegg eeceeteace 780 gacctggtct ttgccttcgc caaccagctg ctgcccctgg agatggatga tgcggagacg 840

28/299

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Arg	Gln	Pro 35	Ser	Pro	Ser	Pro	Ser 40	Pro	Thr	Glu	Arg	Ala 45	Pro	Ala	Ser	
Glu	Glu 50	Glu	Phe	Gln	Phe	Leu 55	Arg	Сув	Gln	Gln	Сув 60	Gln	Ala	Glu	Ala	
Lys 65	Сув	Pro	Lys	Leu	Leu 70	Pro	Cys	Leu	His	Thr 75	Leu	Cys	Ser	Gly	Cys 80	
Leu	Glu	Ala	Ser	Gly 85	Met	Gln	Cys	Pro	Ile 90	Сув	Gln	Ala	Pro	Trp 95	Pro	
Leu	Gly	Ala	Asp 100	Thr	Pro	Ala	Leu	Asp 105	Asn	Val	Phe	Phe	Glu 110	Ser	Leu	
Gl.n	Arg	Arg 115	Leu	Ser	Val	Tyr	Arg 120	Gln	Ile	Val	Asp	Ala 125	Gln	Ala	Val	
Cys	Thr 130		Cys	_	Glu			Asp			Cys 140		Glu	Cys	Glu	
Gln 145	Leu	Leu	Cys	Ala	Lys 150	Cys	Phe	Glu	Ala	His 155	Gln	Trp	Phe	Leu	Lys 160	
His	Glu	Ala	Arg	Pro 165	Leu	Ala	Glu	Leu	Arg 170	Asn	Gln	Ser	Val	Arg 175	Glu	
Phe	Leu	Asp	Gly 180	Thr	Arg	Lys	Thr	Asn 185	Asn	Ile	Phe	Сув	Ser 190	Asn	Pro	
Asn	His	Arg 195	Thr	Pro	Thr	Leu	Thr 200	Ser	Ile	Tyr	Cys	Arg 205	Gly	Cys	Ser	
Lys	Pro 210	Leu	Cys	Сув	Ser	Cys 215	Ala	Leu	Leu	Asp	Ser 220	Ser	His	Ser	Glu	

29/299

Leu Lys Cys Asp Ile Ser Ala Glu Ile Gln Gln Arg Gln Glu Glu Leu Asp Ala Met Thr Gln Ala Leu Gln Glu Gln Asp Ser Ala Phe Gly Ala Val His Ala Gln Met His Ala Ala Val Gly Gln Leu Gly Arg Ala Arg Ala Glu Thr Glu Glu Leu Ile Arg Glu Arg Val Arg Gln Val Val Ala His Val Arg Ala Gln Glu Arg Glu Leu Leu Glu Ala Val Asp Ala Arg Tyr Gln Arg Asp Tyr Glu Glu Met Ala Ser Arg Leu Gly Arg Leu Asp 310 315 Ala Val Leu Gln Arg Ile Arg Thr Gly Ser Ala Leu Val Gln Arg Met 330 Lys Cys Tyr Ala Ser Asp Gln Glu Val Leu Asp Met His Gly Phe Leu Arg Gln Ala Leu Cys Arg Leu Arg Gln Glu Glu Pro Gln Ser Leu Gln Ala Ala Val Arg Thr Asp Gly Phe Asp Glu Phe Lys Val Arg Leu Gln Asp Leu Ser Ser Cys Ile Thr Gln Gly Lys Ala Ile Glu Thr Gln Ser Ser Ser Ser Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro Leu Pro Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn Asp Arg Asn Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu Ser Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg Lys Ala His Gln Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr Thr

30/299

530 535 540 Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu Trp 555 Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp Gln 585 Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg Ile 600 Cys Thr Arg Tyr Thr Pro Glu Gln Asp' Thr Met Thr Phe Ser Asp Gly 615 Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro Leu 630 Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu Met 645 650 Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys Gly 665 Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln Glu 680 Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro Ser Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn Ser Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Arg Asp Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu Ser Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro 790

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<211> 3036

<212> DNA

<213> Homo sapiens

<400> 49

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	cggaagccaa					
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	ccgccctgga					
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	agtgcgagca					
	aggcccggcc					
	gcaagaccaa					
	tctactgccg					
	acagtgagct					
	ccatgacgca					
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	gcgtgcgcca					
	acgcgcggta					
	tgctgcagcg					
	accaggaggt					
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	gcctgcagga					
	gttctgaaga					
	cttgctttgt					
	gctgcaaggg					
	acaagaactg					
	agtgctttga					
	aggaggtgcc					
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	ccggcttcac					
	acatcctgat					
	cggacgggct					
	acctggtctt					
	ggctgctcag					
	gggtggacat					
	ggcccagccg					
	tcagcgccaa					
	cgcctctcat					
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	gcctcagccc					
	cacatggaca					
	gaccccgcac					
	gggacgggga					
	cctgctccca					
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	agctcaccac					
-	cacaagccat					
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<212> PRT

<213> Homo sapiens

<400> 50

32/299

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33/299

Glu Asp Leu Asp Asp Leu Leu Tyr Ala Ala Glu Ile Leu Glu Ile Glu 105 Tyr Leu Glu Glu Gln Cys Leu Lys Met Leu Glu Thr Ile Gln Ala Ser Asp Asp Asn Asp Thr Glu Ala Thr Met Ala Asp Gly Gly Ala Glu Glu Glu Glu Asp Arg Lys Ala Arg Tyr Leu Lys Asn Ile Phe Ile Ser Lys His Ser Ser Glu Glu Ser Gly Tyr Ala Ser Val Ala Gly Gln Ser Leu 170 Pro Gly Pro Met Val Asp Gln Ser Pro Ser Val Ser Thr Ser Phe Gly Leu Ser Ala Met Ser Pro Thr Lys Ala Ala Val Asp Ser Leu Met Thr 200 Ile Gly Gln Ser Leu Leu Gln Gly Thr Leu Gln Pro Pro Ala Gly Pro 210 215 Glu Glu Pro Thr Leu Ala Gly Gly Gly Arg His Pro Gly Val Ala Glu 230 Val Lys Thr Glu Met Met Gln Val Asp Glu Val Pro Ser Gln Asp Ser 245 250 Pro Gly Ala Ala Glu Ser Ser Ile Ser Gly Gly Met Gly Asp Lys Val Glu Glu Arg Gly Lys Glu Gly Pro Gly Thr Pro Thr Arg Ser Ser Val Ile Thr Ser Ala Arg Glu Leu His Tyr Gly Arg Glu Glu Ser Ala Glu Gln Val Pro Pro Pro Ala Glu Ala Gly Gln Ala Pro Thr Gly Arg Pro Glu His Pro Ala Pro Pro Pro Glu Lys His Leu Gly Ile Tyr Ser Val Leu Pro Asn His Lys Ala Asp Ala Val Leu Ser Met Pro Ser Ser Val 345 Thr Ser Gly Leu His Val Gln Pro Ala Leu Ala Val Ser Met Asp Phe Ser Thr Tyr Gly Gly Leu Leu Pro Gln Gly Phe Ile Gln Arg Glu Leu Phe Ser Lys Leu Gly Glu Leu Ala Val Gly Met Lys Ser Glu Ser Arg

Thr Ile Gly Glu Gln Cys Ser Val Cys Gly Val Glu Leu Pro Asp Asn

. 34/299

405 410 415 Glu Ala Val Glu Gln His Arg Lys Leu His Ser Gly Met Lys Thr Tyr 425 Gly Cys Glu Leu Cys Gly Lys Arg Phe Leu Asp Ser Leu Arg Leu Arg Met His Leu Leu Ala His Ser Ala Ile Glu Thr Gln Ser Ser Ser Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro Leu Pro Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys Asn Cys Ile Ile 520 Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg Leu Gln Lys Cys 530 535 Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn Asp Arg Asn Lys 550 Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu Ser Tyr Thr Leu 565 570 Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg Lys Ala His Gln Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr Thr Thr Asn Asn 595 Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu Trp Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg Ile Cys Thr Arg 665 Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp Gly Leu Thr Leu Asn Arg Thr Gln Met His Met Ala Gly Phe Gly Pro Leu Thr Asp Leu 695 Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu Met Asp Asp Ala 705 710

35/299

Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys Gly Asp Arg Gln 725 730 735

Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln Glu Pro Leu Leu
740 745 750

Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro Ser Arg Pro His
755 760 765

Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu Arg Ser Ile Ser 770 775 780

Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met Glu Ile Pro Gly 785 790 795 800

Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn Ser Glu Gly Leu 805 810 815

Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg Asp Gly Gly Gly 820 825 830

Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu Ser Pro Ser Ser 835 840 845

Asn Arg Ser Ser Pro Ala Thr His Ser Pro 850 855

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<211> 277

<212> PRT

<213> Homo sapiens

<400> 53

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Asn Gly Tyr Pro Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu 20 25 30

Gly Gly Leu Ser Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu 35 40 45

Pro Val Ser Gly Tyr Ser Thr Pro Ser Pro Ala Thr Gly Ala Lys Ala 50 55

Phe Val Cys Asp Gln Cys Gly Ala Gln Phe Ser Lys Glu Asp Ala Leu 65 70 75 80

Glu Thr His Arg Gln Thr His Thr Gly Thr Asp Met Ala Val Phe Cys
85 90 95

Leu Leu Cys Gly Lys Arg Phe Gln Ala Gln Ser Ala Leu Gln Gln His
100 105 110

Met Glu Val His Ala Gly Val Arg Ser Tyr Ile Cys Ser Glu Cys Asn 115 120 125

36/299

Arg Thr Phe Pro Ser His Thr Ala Leu Lys Arg His Leu Arg Ser His 130 140

Thr Gly Asp His Pro Tyr Glu Cys Glu Phe Cys Gly Ser Cys Phe Arg 145 150 155 160

Asp Glu Ser Thr Leu Lys Ser His Lys Arg Ile His Thr Gly Glu Lys 165 170 175

Pro Tyr Glu Cys Asn Gly Cys Asp Lys Lys Phe Ser Leu Lys His Gln
180 185 190

Leu Glu Thr His Tyr Arg Val His Thr Gly Glu Lys Pro Phe Glu Cys 195 200 205

Lys Leu Cys His Gln Arg Ser Arg Asp Tyr Ser Ala Met Ile Lys His 210 215 220

Leu Arg Thr His Asn Gly Ala Ser Pro Tyr Gln Cys Thr Ile Cys Thr 225 230 235 240

Glu Tyr Cys Pro Ser Leu Ser Ser Met Gln Lys His Met Lys Gly His 245 250 255

Lys Pro Glu Glu Ile Pro Pro Asp Trp Arg Ile Glu Lys Thr Tyr Leu 260 265 270

Tyr Leu Cys Tyr Val 275

<210> 54

<211> 2311

<212> PRT

<213> Homo sapiens

<400> 54

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Gln Arg Val Pro Ala Leu Leu Pro Pro Gly Pro Pro Val Gly Gly 35 40 45

Gly Gly Pro Gly Ala Pro Pro Ser Pro Pro Ala Val Ala Ala Ala Ala 50 60

Ala Ala Gly Ser Ser Gly Ala Gly Val Pro Gly Gly Ala Ala Ala 65 70 75 80

Ser Ser Ala Ser Ser Gly Pro Ala Leu Leu Arg Val Gly Pro Gly Phe
100 105 110

37/299

Asp Ala Ala Leu Gln Val Ser Ala Ala Ile Gly Thr Asn Leu Arg Arg 120 Phe Arg Ala Val Phe Gly Glu Ser Gly Gly Gly Gly Ser Gly Glu 135 Leu Thr Thr Gln Ile Pro Cys Ser Trp Arg Thr Lys Gly His Ile His Asp Lys Lys Thr Glu Pro Phe Arg Leu Leu Ala Trp Ser Trp Cys Leu Asn Asp Glu Gln Phe Leu Gly Phe Gly Ser Asp Glu Glu Val Arg Val Arg Ser Pro Thr Arg Ser Pro Ser Val Lys Thr Ser Pro Arg Lys Pro 200 Arg Gly Arg Pro Arg Ser Gly Ser Asp Arg Asn Ser Ala Ile Leu Ser 215 Asp Pro Ser Val Phe Ser Pro Leu Asn Lys Ser Glu Thr Lys Ser Gly 230 235 Asp Lys Ile Lys Lys Lys Asp Ser Lys Ser Ile Glu Lys Lys Arg Gly 245 250 Arg Pro Pro Thr Phe Pro Gly Val Lys Ile Lys Ile Thr His Gly Lys Asp Ile Ser Glu Leu Pro Lys Gly Asn Lys Glu Asp Ser Leu Lys Lys Ile Lys Arg Thr Pro Ser Ala Thr Phe Gln Gln Ala Thr Lys Ile Lys Lys Leu Arg Ala Gly Lys Leu Ser Pro Leu Lys Ser Lys Phe Lys Thr Gly Lys Leu Gln Ile Gly Arg Lys Gly Val Gln Ile Val Arg Arg Arg Gly Arg Pro Pro Ser Thr Glu Arg Ile Lys Thr Pro Ser Gly Leu Leu Ile Asn Ser Glu Leu Glu Lys Pro Gln Lys Val Arg Lys Asp Lys Glu Gly Thr Pro Pro Leu Thr Lys Glu Asp Lys Thr Val Val Arg Gln Ser 375 Pro Arg Arg Ile Lys Pro Val Arg Ile Ile Pro Ser Ser Lys Arg Thr 385 Asp Ala Thr Ile Ala Lys Gln Leu Leu Gln Arg Ala Lys Lys Gly Ala

38/299

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Lys	Thr	Gln 435	Val	Lys	Asn	Ile	Arg 440	Gln	Phe	Ile	Met	Pro 445	Val	Val	Ser
Ala	Ile 450	Ser	Ser	Arg	Ile	Ile 455	Lys	Thr	Pro	Arg	Arg 460	Phe	Ile	Glu	Asp
Glu 465	Asp	Tyr	Asp	Pro	Pro 470	Ile	Lys	Ile	Ala	Arg 475	Leu	Glu	Ser	Thr	Pro 480
Asn	Ser	Arg	Phe	Ser 485	Ala	Pro	Ser	Cys	Gly 490	Ser	Ser	Glu	Lys	Ser 495	Ser
Ala	Ala	Ser	Gln 500	His	Ser	Ser	Gln	Met 505	Ser	Ser	Asp	Ser	Ser 510	Arg	Ser
Ser	Ser	Pro 515	Ser	Val	Asp	Thr	Ser 520	Thr	Asp	Ser	Gln	Ala 525	Ser	Glu	Glu
Ile	Gln 530	Val	Leu	Pro	Glu	Glu 535	Arg	Ser	Asp	Thr	Pro 540	Glu	Val	His	Pro
Pro 545	Leu	Pro	Ile	Ser	Gln 550	Ser	Pro	Glu	Asn	Glu 555	Ser	Asn	Asp	Arg	Arg 560
Ser	Arg	Arg	Tyr	Ser 565	Val	Ser	Glu	Arg	Ser 570	Phe	Gly	Ser	Arg	Thr 575	Thr
Lys	Lys	Leu	Ser 580	Thr	Leu	Gln	Ser	Ala 585	Pro	Gln	Gln	Gln	Thr 590	Ser	Ser
Ser	Pro	Pro 595	Pro	Pro	Leu	Leu	Thr 600	Pro	Pro	Pro	Pro	Leu 605	Gln	Pro	Ala
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Phe	Asp 690	Asn	Phe	Arg	Pro	Pro 695	Pro	Leu	Thr	Pro	Glu 700	Asp	Val	Gly	Phe
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39/299

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40/299

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- Leu Pro Met Thr Asp Lys Arg Val Ala Ser Leu Leu Lys Lys Ala Lys
  1060 1065 1070
- Ala Gln Leu Cys Lys Ile Glu Lys Ser Lys Ser Leu Lys Gln Thr Asp 1075 1080 1085
- Gln Pro Lys Ala Gln Gly Gln Glu Ser Asp Ser Ser Glu Thr Ser Val 1090 1095 1100
- Arg Gly Pro Arg Ile Lys His Val Cys Arg Arg Ala Ala Val Ala Leu 1105 1110 1115 1120
- Gly Arg Lys Arg Ala Val Phe Pro Asp Asp Met Pro Thr Leu Ser Ala 1125 1130 1135
- Leu Pro Trp Glu Glu Arg Glu Lys Ile Leu Phe Ser Met Gly Asn Asp 1140 1145 1150
- Asp Lys Ser Ser Ile Ala Gly Ser Glu Asp Ala Glu Pro Leu Ala Pro 1155 1160 1.165
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- Pro Pro Val Lys Lys Gly Arg Arg Ser Arg Arg Cys Gly Gln Cys Pro 1185 1190 1195 1200
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- Lys Pro Lys Phe Gly Gly Arg Asn Ile Lys Lys Gln Cys Cys Lys Met 1220 1225 1230
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- Lys Ser Ser Ser Glu Pro Pro Pro Arg Lys Pro Val Glu Glu Lys Ser 1300 1305 1310
- Glu Glu Gly Asn Val Ser Ala Pro Gly Pro Glu Ser Lys Gln Ala Thr 1315 1320 1325
- Thr Pro Ala Ser Arg Lys Ser Ser Lys Gln Val Ser Gln Pro Ala Leu 1330 1335 1340

41/299

Val Ile Pro Pro Gln Pro Pro Thr Thr Gly Pro Pro Arg Lys Glu Val 1345 1350 1355 1360

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- Glu Ser Gly Pro Glu Gln Ser Lys Gln Lys Lys Val Ala Pro Arg Pro 1380 1385 1390
- Ser Ile Pro Val Lys Gln Lys Pro Lys Glu Lys Glu Lys Pro Pro Pro 1395 1400 1405
- Val Asn Lys Gln Glu Asn Ala Gly Thr Leu Asn Ile Phe Ser Thr Leu 1410 1415 1420
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- Arg Ile Arg Val Asp Phe Lys Gln Thr Tyr Ser Asn Glu Val His Cys 1445 1450 1455
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- Pro Thr Lys Asp Ser Gln His Val Ser Ser Val Thr Gln Asn Gln Lys 1490 1495 1500
- Gln Tyr Asp Thr Ser Ser Lys Thr His Ser Asn Ser Gln Gln Gly Thr 1505 1510 1515 1520
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- Thr Pro Ala Pro Glu Pro Glu Pro Pro Thr Thr Asn Lys Trp Gln Leu 1605 1610 1615
- Asp Asn Trp Leu Thr Lys Val Ser Ser Gln Leu Arg His Gln Arg Ala 1620 1625 1630
- Pro Gly Ala Gln Ser Pro His Gly Gly Thr Gln Arg Val Arg Ala Ala 1635 1640 1645
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42/299

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43/299

Pro Val Ser Ser Ser Ser Gln Lys Pro Ala Lys Pro Ala Leu Lys Arg 1970 1975 1980

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Ser Ser Thr Lys Ser Asn His Lys Asp Ser Ser Ile Pro Lys Gln Arg 2005 2010 2015

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Ile Met Ser Leu Lys Ser Phe Ser Asp Ala Thr Ala Pro Thr Gln Glu 2130 2135 2140

Lys Ile Phe Ala Val Leu Cys Met Arg Cys Gln Ser Ile Leu Asn Met 2145 2150 2155 2160

Ala Met Phe Arg Cys Lys Lys Asp Ile Ala Ile Lys Tyr Ser Arg Thr 2165 2170 2175

Leu Asn Lys His Phe Glu Ser Ser Ser Lys Val Ala Gln Ala Pro Ser 2180 2185 2190

Pro Cys Ile Ala Arg Ser Thr Gly Thr Pro Ser Pro Leu Ser Pro Met 2195 2200 2205

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Gly Ser Ser Gly Val Ala Ala Thr Ile Ser Thr Pro Val Thr Ile Gln 2225 2230 2235 2240

Asn Met Thr Ser Ser Tyr Val Thr Ile Thr Ser His Val Leu Thr Ala 2245 2250 2255

Phe Asp Leu Trp Glu Gln Ala Glu Ala Leu Thr Arg Lys Asn Lys Glu 2260 2265 2270

44/299

Phe Phe Ala Arg Leu Ser Thr Asn Val Cys Thr Leu Ala Leu Asn Ser 2275 2280 2285

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46/299

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47/299

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48/299

His Thr Pro Ser Thr Ala Glu Pro Ser Lys Phe Pro Phe Pro Thr Lys Asp Ser Gln His Val Ser Ser Val Thr Gln Asn Gln Lys Gln Tyr Asp Thr Ser Ser Lys Thr His Ser Asn Ser Gln Gln Gly Thr Ser Ser Met 90 Leu Glu Asp Asp Leu Gln Leu Ser Asp Ser Glu Asp Ser Asp Ser Glu 105 100 Gln Thr Pro Glu Lys Pro Pro Ser Ser Ser Ala Pro Pro Ser Ala Pro 120 Gln Ser Leu Pro Glu Pro Val Ala Ser Ala His Ser Ser Ser Ala Glu Ser Glu Ser Thr Ser Asp Ser Asp Ser Ser Ser Ser Glu Ser Glu Ser Ser Ser Ser <210> 59 <211> 495 <212> DNA <213> Homo sapiens <400> 59 gcaaacagaa aaaagtggct ccccgcccaa gtatccctgt aaaacaaaaa ccaaaagaaa 60 agcagaccta ctccaatgaa gtccattgtg ttgaagagat tctgaaggaa atgacccatt 120 catggccgcc tcctttgaca gcaatacata cgcctagtac agctgagcca tccaagtttc 180 ctttccctac aaaggactct cagcatgtca gttctgtaac ccaaaaccaa aaacaatatg 240 atacatette aaaaacteae teaaattete ageaaggaae gteateeatg etegaagaeg 300 accttcaget cagtgacagt gaggacagtg acagtgaaca aaccccagag aagcctccct 360 cctcatctgc acctccaagt gctccacagt cccttccaga accagtggca tcagcacatt 420 ccagcagtgc agagtcagaa agcaccagtg actcagacag ttcctcagac tcagagagcg 480 agagcagttc aagtg 495 <210> 60 <211> 246 <212> PRT <213> Homo sapiens <400> 60 Lys Gln Lys Lys Val Ala Pro Arg Pro Ser Ile Pro Val Lys Gln Lys Pro Lys Glu Lys Glu Lys Pro Pro Pro Val Asn Lys Gln Glu Asn Ala Gly Thr Leu Asn Ile Leu Ser Thr Leu Ser Asn Gly Asn Ser Ser Lys Gln Lys Ile Pro Ala Asp Gly Val His Arg Ile Arg Val Asp Phe Lys 55

49/299

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50/299

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Glu Gln Thr Tyr Ser Asn Glu Val His Cys Val Glu Glu Ile Leu Lys

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63/299

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### 66/299

Arg Asn Arg Glu Glu Ala Asp Met Trp Thr Thr Phe Arg Pro Arg Ser 250 245 Ser Ser Asn Ala Ser Ser Val Ser Thr Arg Leu Ser Pro Leu Arg Pro 265 Glu Ser Glu Val Leu Ala Glu Glu Ile Pro Ala Ser Val Ser Ser Tyr 280 Ala Gly Gly Val Pro Pro Thr Leu Asn Glu Gly Leu Glu Leu Leu Asp 295 Gly Leu Asn Leu Thr Ser Ser His Ser Leu Leu Ser Arg Ser Gly Leu Ser Gly Phe Ser Leu Gln His Pro Gly Val Thr Gly Pro Leu His Thr 330 Tyr Ser Ser Ser Leu Phe Ser Pro Ala Glu Gly Pro Leu Ser Ala Gly Glu Gly Cys Phe Ser Ser Gln Ala Leu Glu Ala Leu Leu Thr Ser 360 Asp Thr Pro Pro Pro Pro Ala Asp Val Leu Met Thr Gln Val Asp Pro 375 Ile Leu Ser Gln Ala Pro Thr Leu Leu Leu Gly Gly Leu Pro Ser Ser Ser Lys Leu Ala Thr Gly Val Gly Leu Cys Pro Lys Pro Leu Glu Ala Arg Gly Pro Ser Ser Leu Val Pro Thr Leu Ser Met Ile Ala Pro Pro Pro Val Met Ala Ser Ala Pro Ile Pro Lys Ala Leu Gly Thr Pro 440 Val Leu Thr Pro Pro Thr Glu Ala Ala Ser Gln Asp Arg Met Pro Gln 455 Asp Leu Asp Leu Asp Met Tyr Met Glu Asn Leu Glu Cys Asp Met Asp 465 . 470 475 Asn Ile Ile Ser Asp Leu Met Asp Glu Gly Glu Gly Leu Asp Phe Asn 485 490

Phe Glu Pro Asp Pro 500

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ggaacctctg caga
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<211> 22
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<213> Homo sapiens
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Glu Ile Leu Phe Ser Arg
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<210> 84
<211> 69
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70/299

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Lys Val Ser Ser Ser Ala Ser Ser Ser Ser His His Glu Ala Ser Thr 275 280 285

Gln Glu Thr Ser Glu Ser Ser Arg Glu Ser Lys Gly Lys Lys Ser Ser

295

71/299

Ser His Ser Leu Ser His Lys Gly Lys Lys Leu Ser Ser Gly Lys Gly 310 315 Val Ser Ser Phe Thr Ser Ala Ser Ser Ser Ser Ser Ser Ser Ser 325 330 Ser Ser Gly Gly Pro Phe Gln Pro Ala Val Ser Ser Leu Gln Ser Ser 345 Pro Asp Phe Ser Ala Phe Pro Lys Leu Glu Gln Pro Glu Glu Asp Lys Tyr Ser Lys Pro Thr Ala Pro Ala Pro Ser Ala Pro Pro Ser Pro Ser 375 Ala Pro Glu Pro Pro Lys Ala Asp Leu Phe Glu Gln Lys Val Val Phe Ser Gly Phe Gly Pro Ile Met Arg Phe Ser Thr Thr Thr Ser Ser Ser 410 Gly Arg Ala Arg Ala Pro Ser Pro Gly Asp Tyr Lys Ser Pro His Val 425 Thr Gly Ser Gly Ala Ser Ala Gly Thr His Lys Arg Met Pro Ala Leu 440 Ser Ala Thr Pro Val Pro Ala Asp Glu Thr Pro Glu Thr Gly Leu Lys 450 455 Glu Lys Lys His Lys Ala Ser Lys Arg Ser Arg His Gly Pro Gly Arg Pro Lys Gly Ser Arg Asn Lys Glu Gly Thr Gly Gly Pro Ala Ala Pro Ser Leu Pro Ser Ala Gln Leu Ala Gly Phe Thr Ala Thr Ala Ala Ser Pro Phe Ser Gly Gly Ser Leu Val Ser Ser Gly Leu Gly Gly Leu Ser Ser Arg Thr Phe Gly Pro Ser Gly Ser Leu Pro Ser Leu Ser Leu Glu Ser Pro Leu Gly Ala Gly Ile Tyr Thr Ser Asn Lys Asp Pro Ile 555 Ser His Ser Gly Gly Met Leu Arg Ala Val Cys Ser Thr Pro Leu Ser 570 Ser Ser Leu Leu Gly Pro Pro Gly Thr Ser Ala Leu Pro Arg Leu Ser 585 Arg Ser Pro Phe Thr Ser Thr Leu Pro Ser Ser Ser Ala Ser Ile Ser Thr Thr Gln Val Phe Ser Leu Ala Gly Ser Thr Phe Ser Leu Pro Ser

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Thr 625	His	Ile	Phe	Gly	Thr 630	Pro	Met	Gly	Ala	Val 635	Asn	Pro	Leu	Leu	Ser 640
Gln	Ala	Glu	Ser	Ser 645	His	Thr	Glu	Pro	Asp 650	Leu	Glu	Asp	Сув	Ser 655	Phe
Arg	Cys	Arg	Gly 660	Thr	Ser	Pro	Gln	Glu 665	Ser	Leu	Ser	Ser	Met 670	Ser	Pro
Ile	Ser	Ser 675	Leu	Pro	Ala	Leu	Phe 680	Asp	Gln	Thr	Ala	Ser 685	Ala	Pro	Cys
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Glu	Met	Leu	Lys	Ala 725	Leu	His	Ala	Leu	Gln 730	Lys	Glu	Asn	Gln	Arg 735	Leu
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His	Ser	Gly	Cys 820	Pro	Ser	Arg	Ser	Ser 825	Ser	Ser	Leu	Ser	Phe 830	His	Ser
Thr	Pro	Pro 835	Pro	Leu	Pro	Leu	Leu 840	Gln	Gln	Ser	Pro	Ala 845	Thr	Leu	Pro
Leu	Ala 850	Leu	Pro	Gly	Ala	Pro 855	Ala	Pro	Leu	Pro	Pro 860	Gln	Pro	Gln	Asn
Gly 865	Leu	Gly	Arg	Ala	Pro 870	Gly	Ala	Ala	Gly	Leu 875	Gly	Ala	Met	Pro	Met 880
Ala	Glu	Gly	Leu	Leu 885	Gly	Gly	Leu	Ala	Gly 890	Ser	Gly	Gly	Leu	Pro 895	Leu
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73/299

Leu Asn Ser Leu Thr Glu Gln Gln Arg His Leu Leu Gln Gln Gln Glu 930 935 Gln Gln Leu Gln Gln Leu Gln Leu Leu Ala Ser Pro Gln Leu Thr 950 955 Pro Glu His Gln Thr Val Val Tyr Gln Met Ile Gln Gln Ile Gln Gln 965 970 Lys Arg Glu Leu Gln Arg Leu Gln Met Ala Gly Gly Ser Gln Leu Pro 985 Met Ala Ser Leu Leu Ala Gly Ser Ser Thr Pro Leu Leu Ser Ala Gly 1000 Thr Pro Gly Leu Leu Pro Thr Ala Ser Ala Pro Pro Leu Leu Pro Ala 1015 1020 Gly Ala Leu Val Ala Pro Ser Leu Gly Asn Asn Thr Ser Leu Met Ala 1025 1030 1035 1045 1050 Leu Thr Ala Gln Thr Asn Pro Phe Leu Ser Leu Ser Gly Ala Glu Gly 1060 1065 Ser Gly Gly Pro Lys Gly Gly Thr Ala Asp Lys Gly Ala Ser Ala 1080 Asn Gln Glu Lys Gly 1090 <210> 92 <211> 3282 <212> DNA <213> Homo sapiens <400> 92 atgaaggaga tggtaggagg ctgctgcgta tgttcggacg agaggggctg ggccgagaac 60 ccgctggtct actgcgatgg gcacgcgtgc agcgtggccg tccaccaagc ttgctatggc 120 ategtteagg tgecaaeggg accetggtte tgeeggaaat gtgaatetea ggagegagea 180 gccagggtga ggtgtgagct gtgcccacac aaagacgggg cattgaagag gactgataat 240 ggaggctggg cacacgtggt gtgtgccctc tacatccccg aggtgcaatt tgccaacgtg 300 ctcaccatgg agcccatcgt gctgcagtac gtgcctcatg atcgcttcaa caaqacctqt 360 tacatctgcg aggagacggg ccgggagagc aaggcqqcct cggqaqcctq catqacctqt 420 aaccgccatg gatgtcgaca agctttccac gtcacctgtg cccaaatggc aggcttgctq 480 tgtgaggaag aagtgctgga ggtggacaac gtcaagtact gcggctactg caaataccac 540 ttcagcaaga tgaagacatc ccggcacagc agcgggggag gcggaggagg cgctggagga 600 ggaggtggca gcatgggggg aggtggcagt ggtttcatct ctgggaggag aagccggtca 660 gcctcaccat ccacgcagca ggagaagcac cccacccacc acgagagggg ccagaagaag 720 agtcgaaagg acaaagaacg ccttaagcag aagcacaaga agcggcctga gtcgccccc 780 ageatectea eccegeeegt ggteeceact getgacaagg tetecteete ggetteetet 840 tecteccace acgaggecag cacgeaggag acctetgaga geageaggga gteaaagggg 900

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<213> Homo sapiens

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Ala Pro Asp Ala Gly Ala Ala Leu Ala Gly Lys Leu Arg Ser Gly Asp \$35\$

Arg Ser Met Val Glu Val Leu Ala Asp His Pro Gly Glu Leu Val Arg 50 55 60

Thr 65	Asp	Ser	Pro	Asn	Phe 70	Leu	Cys	Ser	Val	Leu 75	Pro	Thr	His	Trp	Arg 80
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Val	Pro	Asp	Gly 100	Thr	Leu	Val	Thr	Val 105	Met	Ala	Gly	Asn	Asp 110	Glu	Asn
Tyr	Ser	Ala 115	Glu	Leu	Arg	Asn	Ala 120	Thr	Ala	Ala	Met	Lys 125	Asn	Gln	Val
Ala	Arg 130	Phe	Asn	Asp	Leu	Arg 135	Phe	Val	Gly	Arg	Ser 140	Gly	Arg	Gly	Lys
Ser 145	Phe	Thr	Leu	Thr	Ile 150	Thr	Val	Phe	Thr	Asn 155	Pro	Pro	Gln	Val	Ala 160
Thr	Tyr	His	Arg	Ala 165	Ile	Lys	Ile	Thr	Val 170	Asp	Gly	Pro	Arg	Glu 175	Pro
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Val	Lys	Thr 195	Gln	Ser	Arg	Leu	Thr 200	Pro	Pro	Thr	Met	Pro 205	Pro	Pro	Pro
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Pro	Pro	Asn	Gly	Phe 245	Ser	Asn	Gly	Pro	Ser 250	Ser	Ser	Ser	Ser	Ser 255	Ser
Leu	Ala	Asn	Gln 260	Gln	Leu	Pro	Pro	Ala 265	Cys	Gly	Ala	Arg	Gln 270	Leu	Ser
ГХв	Leu	Lys 275	Arg	Phe	Leu	Thr	Thr 280	Leu	Gln	Gln	Phe	Gly 285	Asn	Asp	Ile
Ser	Pro 290	Glu	Ile	Gly	Glu	Arg 295	Val	Arg	Thr	Leu	Val 300	Leu	Gly	Leu	Val
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Thr	Asn	Phe	Pro	Leu 325	Arg	Pro	Phe	Val	Ile 330	Pro	Phe	Leu	Lys	Ala 335	Asn
Leu	Pro	Leu	Leu 340	Gln	Arg	Glu	Leu	Leu 345	His	Сув	Ala	Arg	Leu 350	Ala	Lys
Gln	Asn	Pro 355	Ala	Gln	Tyr	Leu	Ala 360	Gln	His	Glu	Gln	Leu 365	Leu	Leu	Asp
Ala	Ser	Thr	Thr	Ser	Pro	Val	qaA	Ser	Ser	Glu	Leu	Leu	Leu	qaA	Val

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Phe	Asp	Arg	Glu	Pro 405	Leu	His	Ser	Glu	His 410	Pro	Ser	Lys	Arg	Pro 415	Cys
Thr	Ile	Ser	Pro 420	Gly	Gln	Arg	Tyr	Ser 425	Pro	Asn	Asn	Gly	Leu 430	Ser	Tyr
Gln	Pro	Asn 435	Gly	Leu	Pro	His	Pro 440	Thr	Pro	Pro	Pro	Pro 445	Gln	His	Tyr
Arg	Leu 450	Asp	Asp	Met	Ala	Ile 455	Ala	His	His	Tyr	Arg 460	Asp	Ser	Tyr	Arg
His 465	Pro	Ser	His	Arg	Asp 470	Leu	Arg	Asp	Arg	Asn 475	Arg	Pro	Met	Gly	Leu 480
His	Gly	Thr	Arg	Gln 485	Glu	Glu	Met	Ile	Asp 490	His	Arg	Leu	Thr	Asp 495	Arg
Glu	Trp	Ala	Glu 500	Glu	Trp	Lys	His	Leu 505	Asp	His	Leu	Leu	Asn 510	Cys	Ile
Met	Asp	Met 515	Val	Glu	Lys	Thr	Arg 520	Arg	Ser	Leu	Thr	Val 525	Leu	Arg	Arg
Cys	Gln 530	Glu	Ala	Asp	Arg	Glu 535	Glu	Leu	Asn	Tyr	Trp 540	Ile	Arg	Arg	Tyr
Ser 545	Asp	Ala	Glu	Asp	Leu 550	Lys	Lys	Gly	Gly	Gly 555	Ser	Ser	Ser	Ser	His 560
Ser	Arg	Gln	Gln	Ser 565	Pro	Val	Asn	Pro	Asp 570	Pro	Val	Ala	Leu	Asp 575	Ala
His	Arg	Glu	Phe 580	Leu	His	Arg	Pro	Ala 585	Ser	Gly	Tyr	Val	Pro 590	Glu	Glu
Ile	Trp	Ьув 595	Lys	Ala	Glu	Glu	Ala 600	Val	Asn	Glu	Val	Lуs 605	Arg	Gln	Ala
Met	Thr 610	Glu	Leu	Gln	Lys	Ala 615	Val.	Ser	Glu	Ala	Glu 620	Arg	Lys	Ala	His
Asp 625	Met	Ile	Thr	Thr	Glu 630	Arg	Ala	Lys	Met	Glu 635	Arg	Thr	Val	Ala	Glu 640
Ala	Lys	Arg	Gln	Ala 645	Ala	Glu	qaA	Ala	Leu 650	Ala	Val	Ile	Asn	Gln 655	Gln
Glu	Asp	Ser	Ser 660	Glu	Ser	Cys	Trp	Asn 665	Cys	Gly	Arg	Lys	Ala 670	Ser	Glu
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77/299

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79/299

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80/299

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## 81/299

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82/299

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83/299

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85/299

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86/299

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Arg Ser Met Val Glu Val Leu Ala Asp His Pro Gly Glu Leu Val Arg 50 55 60

Thr Asp Ser Pro Asn Phe Leu Cys Ser Val Leu Pro Thr His Trp Arg 65 70 75 80

Cys Asn Lys Thr Leu Pro Ile Ala Phe Lys Val Val Ala Leu Gly Asp 85 90 95

Val Pro Asp Gly Thr Leu Val Thr Val Met Ala Gly Asn Asp Glu Asn 100 105 110

Tyr Ser Ala Glu Leu Arg Asn Ala Thr Ala Ala Met Lys Asn Gln Val 115 120 125

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Pro Tyr Val Gly Glu Gln Arg Ser Asn Leu Lys Asp Pro Ser Tyr Gly

87/299

275 280 Trp Glu Ile Leu Asp Glu Phe Tyr Asn Val Lys Phe Cys Ile Asp Ala 295 Ser Gln Pro Asp Val Gly Ser Trp Leu Lys Tyr Ile Arg Phe Ala Gly Cys Tyr Asp Gln His Asn Leu Val Ala Cys Gln Ile Asn Asp Gln Ile 330 Phe Tyr Arg Val Val Ala Asp Ile Ala Pro Gly Glu Glu Leu Leu Phe Met Lys Ser Glu Asp Tyr Pro His Glu Thr Met Ala Pro Asp Ile 360 His Glu Glu Arg Gln Tyr Arg Cys Glu Asp Cys Asp Gln Leu Phe Glu Ser Lys Ala Glu Leu Ala Asp His Gln Lys Phe Pro Cys Ser Thr Pro His Ser Ala Phe Ser Met Val Glu Glu Asp Phe Gln Gln Lys Leu Glu 410 Ser Glu Asn Asp Leu Gln Glu Ile His Thr Ile Gln Glu Cys Lys Glu 425 Cys Asp Gln Val Phe Pro Asp Leu Gln Ser Leu Glu Lys His Met Leu 440 Ser His Thr Glu Glu Arg Glu Tyr Lys Cys Asp Gln Cys Pro Lys Ala Phe Asn Trp Lys Ser Asn Leu Ile Arg His Gln Met Ser His Asp Ser 470 475 Gly Lys His Tyr Glu Cys Glu Asn Cys Ala Lys Val Phe Thr Asp Pro 490 Ser Asn Leu Gln Arg His Ile Arg Ser Gln His Val Gly Ala Arg Ala 505 His Ala Cys Pro Glu Cys Gly Lys Thr Phe Ala Thr Ser Ser Gly Leu Lys Gln His Lys His Ile His Ser Ser Val Lys Pro Phe Ile Cys Glu Val Cys His Lys Ser Tyr Thr Gln Phe Ser Asn Leu Cys Arg His Lys Arg Met His Ala Asp Cys Arg Thr Gln Ile Lys Cys Lys Asp Cys Gly 570 Gln Met Phe Ser Thr Thr Ser Ser Leu Asn Lys His Arg Arg Phe Cys 585

Glu	Gly	Lys 595	Asn	His	Phe	Ala	Ala 600	Gly	Gly	Phe	Phe	Gly 605	Gln	Gly	Ile
Ser	Leu 610	Pro	Gly	Thr	Pro	Ala 615	Met	Asp	Lys	Thr	Ser 620	Met	Val	Asn	Met
Ser 625	His	Ala	Asn	Pro	Gly 630	Leu	Ala	Asp	Tyr	Phe 635	Gly	Ala	Asn	Arg	His 640
Pro	Ala	Gly	Leu	Thr 645	Phe	Pro	Thr	Ala	Pro 650	Gly	Phe	Ser	Phe	Ser 655	Phe
Pro	Gly	Leu	Phe 660	Pro	Ser	Gly	Leu	Tyr 665	His	Arg	Pro	Pro	Leu 670	Ile	Pro
Ala	Ser	Ser 675	Pro	Val	Lys	Gly	Leu 680	Ser	Ser	Thr	Glu	Gln 685	Thr	Asn	Lys
Ser	Gln 690	Ser	Pro	Leu	Met	Thr 695	His	Pro	Gln	Ile	Leu 700	Pro	Ala	Thr	Gln
Asp 705	Ile	Leu	Lys	Ala	Leu 710	Ser	Ŀys	His	Pro	Ser 715	Val	Gly	Asp	Asn	Lys 720
Pro	Val	Glu	Leu	Gln 725	Pro	Glu	Arg	Ser	Ser 730	Glu	Glu	Arg	Pro	Phe 735	Glu
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Lуs 785	Asp	Lys	Val	Ser	Pro 790	Leu	Gln	Asn	Leu	Ala 795	Ser	Ile	Asn	Asn	800 PAs
Lys	Glu	Tyr	Ser	Asn 805	His	Ser	Ile	Phe	Ser 810	Pro	Ser	Leu	Glu	Glu 815	Gln
Thr	Ala	Va1	Ser 820	Gly	Ala	Val	Asn	Asp 825	Ser	Ile	Lys	Ala	Ile 830	Ala	Ser
Ile	Ala	Glu 835	Lys	Tyr	Phe	Gly	Ser 840	Thr	Gly	Leu	Val	Gly 845	Leu	Gln	Asp
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89/299

Lys Leu Gln Lys Gly Ser Ser Glu Ser Pro Phe Asp Leu Thr Thr Lys 900 905 910

- Arg Lys Asp Glu Lys Pro Leu Thr Pro Val Pro Ser Lys Pro Pro Val 915 920 925
- Thr Pro Ala Thr Ser Gln Asp Gln Pro Leu Asp Leu Ser Met Gly Ser 930 935 940
- Arg Ser Arg Ala Ser Gly Thr Lys Leu Thr Glu Pro Arg Lys Asn His 945 950 955 960
- Val Phe Gly Gly Lys Lys Gly Ser Asn Val Glu Ser Arg Pro Ala Ser 965 970 975
- Asp Gly Ser Leu Gln His Ala Arg Pro Thr Pro Phe Met Asp Pro 980 985 990
- Ile Tyr Arg Val Glu Lys Arg Lys Leu Thr Asp Pro Leu Glu Ala Leu 995 1000 1005
- Lys Glu Lys Tyr Leu Arg Pro Ser Pro Gly Phe Leu Phe His Pro Gln 1010 1015 1020
- Met Ser Ala Ile Glu Asn Met Ala Glu Lys Leu Glu Ser Phe Ser Ala 1025 1030 1035 1040
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90/299 1205 1210 1215 Phe Lys Asp Glu Lys Ala Leu Val Thr Ser Gln Asn Ser Asp Leu Leu 1225 Asp Asp Glu Glu Val Glu Asp Glu Val Leu Leu Asp Glu Glu Asp Glu 1240 Asp Asn Asp Ile Thr Gly Lys Thr Gly Lys Glu Pro Val Thr Ser Asn 1255 Leu His Glu Gly Asn Pro Glu Asp Asp Tyr Glu Glu Thr Ser Ala Leu 1265 1270 Glu Met Ser Cys Lys Thr Ser Pro Val Arg Tyr Lys Glu Glu Glu Tyr 1290 Lys Ser Gly Leu Ser Ala Leu Asp His Ile Arg His Phe Thr Asp Ser Leu Lys Met Arg Lys Met Glu Asp Asn Gln Tyr Ser Glu Ala Glu Leu 1320 Ser Ser Phe Ser Thr Ser His Val Pro Glu Glu Leu Lys Gln Pro Leu 1335 His Arg Lys Ser Lys Ser Gln Ala Tyr Ala Met Met Leu Ser Leu Ser 1350 1355 Asp Lys Glu Ser Leu His Ser Thr Ser His Ser Ser Ser Asn Val Trp 1365 1370 His Ser Met Ala Arg Ala Ala Glu Ser Ser Ala Ile Gln Ser Ile 1380 1385 Ser His Val 1395 <210> 106 <211> 5938 <212> DNA <213> Homo sapiens <400> 106 tttccaggca ctctcattca tagagccagc gggcgcgggc gggacgggcg ccccgcggcc 60 ggacccagec agggcaccac getgecegge cetgegeege caggcactte ttteegggge 120 tcctagggac gccagaagga agtcaacctc tgctgcttct ccttggcctg cgttggacct 180 tecttttttt gttgtttttt tttgtttttc ccctttcttc cttttgaatt aactggcttc 240 ttggctggat gttttcaact tctttcctgg ctgcgaactt tttccccaat tgttttcctt 300 ttacaacagg gggagaaagt gctctgtggt ccgaggcgag ccgtgaagtt gcgtgtgcgt 360 ggcagtgtgc gtggcaggat gtgcgtgcgt gtgtaacccg agccgcccga tctgtttcga 420 tctgcgccgc ggagccctcc ctcaaggccc gctccacctg cttggcggtt acgcggcgct 480 cgtgggtgtt cgtgccttcg gagcagctaa ccggcgggtg ctgggcgacg gtggaggagt 540 atcgttctcg ctgcttgccc gagtcagggc tgagtcaccc cagctgatgt agacagtggc 600 tgccttccga agagtgcgtg tttgcatgtg tgtgactctg cggctgctca actcccaaca 660 aaccagagga ccagccacaa acttaaccaa catccccaaa cccgagttca cagatgtggg 720

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Thr Pro Pro Ser Thr Ala Leu Ser Pro Gly Lys Met Ser Glu Ala Leu 20 25 30

Pro Leu Gly Ala Pro Asp Ala Gly Ala Ala Leu Ala Gly Lys Leu Arg  $35 \cdot 40$  45

Ser Gly Asp Arg Ser Met Val Glu Val Leu Ala Asp His Pro Gly Glu
50 55 60

Leu Val Arg Thr Asp Ser Pro Asn Phe Leu Cys Ser Val Leu Pro Thr 65 70 75 80

His Trp Arg Cys Asn Lys Thr Leu Pro Ile Ala Phe Lys Val Val Ala 85 90 95

Leu Gly Asp Val Pro Asp Gly Thr Leu Val Thr Val Met Ala Gly Asn 100 105 110

Asp Glu Asn Tyr Ser Ala Glu Leu Arg Asn Ala Thr Ala Ala Met Lys

<sup>&</sup>lt;211> 261

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Homo sapiens

93/299 115 120 125 Asn Gln Val Ala Arg Phe Asn Asp Leu Arg Phe Val Gly Arg Ser Gly 135 Arg Gly Lys Ser Phe Thr Leu Thr Ile Thr Val Phe Thr Asn Pro Pro 145 150 155 Gln Val Ala Thr Tyr His Arg Ala Ile Lys Ile Thr Val Asp Gly Pro 165 170 Arg Glu Pro Arg Arg His Arg Gln Lys Leu Asp Asp Gln Thr Lys Pro 180 1.85 Gly Ser Leu Ser Phe Ser Glu Arg Leu Ser Glu Leu Glu Gln Leu Arg 200 Arg Thr Ala Met Arg Val Ser Pro His His Pro Ala Pro Thr Pro Asn Pro Arq Ala Ser Leu Asn His Ser Thr Ala Phe Asn Pro Gln Pro Gln 230 235 Ser Gln Met Gln Glu Ser Trp Met Leu Pro Ile Leu Ser Ser Phe Cys 245 250 Lys Lys Gly Ser Lys 260 <210> 108 <211> 1025 <212> DNA <213> Homo sapiens <400> 108 atgaateett etagagaegt eeacgatgee ageaegagee geegetteae geegeettee 60 accgegetga geccaggeaa gatgagegag gegttgeege tgggegeece ggaegeegge 120 getgeeetgg eeggeaaget gaggagegge gaeegeagea tggtqgaqqt qetggeeqae 180 caccegggeg agetggtgcg caccgacage eccaacttee tetgeteeqt getgeetacq 240 cactggcgct gcaacaagac cctgcccatc qctttcaagg tqqtqqccct aqqqqatqtt 300 ccagatggca ctctggtcac tgtgatggct ggcaatgatg aaaactactc ggctgagctg 360 agaaatgcta ccgcagccat gaagaaccag gttgcaagat ttaatgacct caggtttqtc 420 ggtcgaagtg gaagagggaa aagettcact etgaccatca etgtetteae aaacccaccq 480 caagtegeca cetaccacag agecateaaa ateacagtgg atgggeeceg agaacetega 540

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1025

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95/299

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<211> 120

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35 40 45

Glu Lys Ser Leu Ile Val Glu Gly Lys Arg Glu Lys Lys Lys Val Glu
50 60

Arg Leu Thr Met Gln Val Ser Ser Leu Gln Arg Glu Pro Phe Thr Ile 65 70 75 80

Ala Gln Gly Lys Gly Gln Lys Leu Cys Glu Ile Glu Arg Ile His Phe 85 90 95

Phe Leu Ser Lys Lys Thr Asp Glu Leu Arg Asn Leu His Lys Leu
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Leu Tyr Asn Arg Pro Gly Thr Val Ser Ser Leu Lys Lys Asn Val Gly
115 120 125

Gln Phe Ser Gly Phe Pro Phe Glu Lys Gly Ser Val Gln Tyr Lys Lys 130  $\,$  135  $\,$  140

Cys Glu Val Leu Asp Leu Glu Arg Ser Gly Val Asn Ser Glu Leu Val 165 170 175

Lys Arg Ile Leu Asn Phe Leu Met His Pro Lys Pro Ser Gly Lys Pro 180 185 190

Leu Pro Lys Ser Lys Lys Thr Cys Ser Lys Gly Ser Lys Glu Arg

Asn Ser Ser Gly Met Ala Arg Lys Ala Lys Arg Thr Lys Cys Pro Glu 210 215 220

96/299

Ile Leu Ser Asp Glu Ser Ser Ser Asp Glu Asp Glu Lys Lys Asn Lys 225 235 Glu Glu Ser Ser Asp Asp Glu Asp Lys Glu Ser Glu Glu Glu Pro Pro 250 245 Lys Lys Thr Ala Lys Arg Glu Lys Pro Lys Gln Lys Ala Thr Ser Lys 265 Ser Lys Lys Ser Val Lys Ser Ala Asn Val Lys Lys Ala Asp Ser Ser 280 Thr Thr Lys Lys Asn Gln Asn Ser Ser Lys Lys Glu Ser Glu Ser Glu 295 Asp Ser Ser Asp Asp Glu Pro Leu Ile Lys Lys Leu Lys Lys Pro Pro 305 Thr Asp Glu Glu Leu Lys Glu Thr Ile Lys Lys Leu Leu Ala Ser Ala 330 Asn Leu Glu Glu Val Thr Met Lys Gln Ile Cys Lys Lys Val Tyr Glu Asn Tyr Pro Thr Tyr Asp Leu Thr Glu Arg Lys Asp Phe Ile Lys Thr 360 Thr Val Lys Glu Leu Ile Ser 370 <210> 116 <211> 2699 <212> DNA <213> Homo sapiens <220> <221> modified base <222> (1740) <223> a, c, t, g, other or unknown ggcccgcggc ggccgaaatc cgcggttcac agcatgtccg cctcggcccc tgctgcggag 60 ggggagggaa cccccaccca gcccgcgtcc gagaaagaac ccgaaatgcc cggtcccaga 120 gaggagagcg aggaggaaga ggacgaggac gacgaggagg aqqaggagga ggaaaaaqaa 180 aagagtetea tegtggaagg caagagggaa aagaaaaaag tagagaggtt gacaatgcaa 240 gtctcttcct tacagagaga gccatttaca attgcacaag gaaaggggca gaaactttgt 300 gaaattgaga ggatacattt ttttctaagt aagaagaaaa ccgatgaact tagaaatcta 360 cacaaactgc tttacaacag gccaggcact gtgtcctcat taaagaagaa tgtgggtcag 420 ttcagtggct ttccatttga aaaaggaagt gtccaatata aaaagaagga agaaatgttg 480 aaaaaattta gaaatgccat gttaaagagc atctgtgagg ttcttgattt ggagagatca 540 ggtgtaaata gtgaactagt gaagaggatc ttgaatttct taatgcatcc aaagccttct 600 agttctggaa tggcaaggaa ggctaagcga accaaatgtc ctgaaattct gtcagatgaa 720 tctagtagtg atgaagatga aaagaaaaac aaggaagagt cttcagatga tgaagataaa 780 gaaagtgaag aggagccacc aaaaaagaca gccaaaagag aaaaacctaa acaqaaaqct 840 acttctaaaa gtaaaaaatc tgtgaaaaqt gccaatqtta aqaaagcaga taqcaqcacc 900 accaagaaga atcaaaacag ttccaaaaaa gaaagtgagt ctgaggatag ttcagatgat 960

### 97/299

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Glu His Ile Asp Glu Val Gln Asn Glu Ile Asp Arg Leu Asn Glu Gln
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40

98/299

Ala Ser Glu Glu Ile Leu Lys Val Glu Gln Lys Tyr Asn Lys Leu Arg Gln Pro Phe Phe Gln Lys Arg Ser Glu Leu Ile Ala Lys Ile Pro Asn Phe Trp Val Thr Thr Phe Val Asn His Pro Gln Val Ser Ala Leu Leu Gly Glu Glu Asp Glu Glu Ala Leu His Tyr Leu Thr Arg Val Glu Val 105 Thr Glu Phe Glu Asp Ile Lys Ser Gly Tyr Arg Ile Asp Phe Tyr Phe 120 Asp Glu Asn Pro Tyr Phe Glu Asn Lys Val Leu Ser Lys Glu Phe His Leu Asn Glu Ser Gly Asp Pro Ser Ser Lys Ser Thr Glu Ile Lys Trp Lys Ser Gly Lys Asp Leu Thr Lys Arg Ser Ser Gln Thr Gln Asn Lys Ala Ser Arg Lys Arg Gln His Glu Glu Pro Glu Ser Phe Phe Thr Trp Phe Thr Asp His Ser Asp Ala Gly Ala Asp Glu Leu Gly Glu Val Ile 200 Lys Asp Asp Ile Trp Pro Asn Pro Leu Gln Tyr Tyr Leu Val Pro Asp 210 215 Met Asp Asp Glu Glu Gly Glu Glu Glu Asp Asp Asp Asp Glu Glu Glu Glu Gly Leu Glu Asp Ile Asp Glu Glu Gly Asp Glu Asp Glu 245 Gly Glu Glu Asp Glu Asp Asp Glu Gly Glu Gly Glu Glu Gly Glu Asp 260 265 Glu Gly Glu Asp Asp 275 <210> 119 <211> 2577 <212> DNA <213> Homo sapiens <400> 119 cacatgtcgg cgcaggcggc caaaqtcaqt aaaaaggagc tcaactccaa ccacqacqqq 60 gccgacgaga cctcagaaaa agaacagcaa gaagcgattg aacacattga tgaagtacaa 120

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99/299

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gatgaagatg														
gaacactgat														
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ggtctctttt														
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gtttctgaaa														
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tgatgtataa														
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1		5					10					15		
Thr Lys Lys	s Thr	Gln	Leu	Gln	Len	Glu	His	Len	Tien	T.e.11	Asp	Tien	Gln	
	20	04.11			200	25	11	a	.iic u.	пси	30		Q.III	
	20					د ے					50			
Met Ile Lei	ı Aer	ദിം	Tle	Δan	Δαν	Тугт	Tare	Δση	Dro	Laze	T.e.i	ጥኤ~	7 200	
		оту.	TTC	USII		TAT	пλя	HPII	PTO	-	псп	THE	ATG	
35	,				40					45				
Mat Las Da	o Dho	T.3	Dha	Пт •••	Met	D	T	T	7.7 -	m1	<b>~</b> 1	T	T	
Met Leu Thi	L Pne	тўв .	Lue		Met	Pro	ьys	тЛг		Thr	GIU	ьeu	ьуs	
50				55					60					

100/299

His Leu Gln Cys Leu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Met Ala Gly Gln Cys Ser Gln Asn Glu Tyr Phe Asp Ser Leu Leu His Ala Cys Ile Pro Cys 120 125 Gln Leu Arg Cys Ser Ser Asn Thr Pro Pro Leu Thr Cys Gln Arg Tyr 135 Cys Asn Ala Ser Val Thr Asn Ser Val Lys Gly Thr Asn Ala Ile Leu 145 150 155 Trp Thr Cys Leu Gly Leu Ser Leu Ile Ile Ser Leu Ala Val Phe Val 165 170 Leu Met Phe Leu Leu Arg Lys Ile Ser Ser Glu Pro Leu Lys Asp Glu 185 Phe Lys Asn Thr Gly Ser Gly Leu Leu Gly Met Ala Asn Ile Asp Leu 200 Glu Lys Ser Arg Thr Gly Asp Glu Ile Ile Leu Pro Arg Gly Leu Glu Tyr Thr Val Glu Glu Cys Thr Cys Glu Asp Cys Ile Lys Ser Lys Pro Lys Val Asp Ser Asp His Cys Phe Pro Leu Pro Ala Met Glu Glu Gly Ala Thr Ile Leu Val Thr Thr Lys Thr Asn Asp Tyr Cys Lys Ser Leu Pro Ala Ala Leu Ser Ala Thr Glu Ile Glu Lys Ser Ile Ser Ala Arq 280 <210> 121 <211> 1073 <212> DNA <213> Homo sapiens <400> 121 gcactaagtc ttgcacttgt cacaaacagt gcacctactt caagttctac aaagaaaaaca 60 cagctacaac tggagcattt actgctggat ttacagatga ttttgaatgg aattaataat 120 tacaagaatc ccaaactcac caggatgetc acatttaagt tttacatgcc caaqaaqqcc 180 acagaactga aacatcttca gtgtctagaa gaagaactca aacctctgga ggaagtgcta 240 aatttagctc aaagcaaaaa ctttcactta agacccaggg acttaatcaq caatatcaac 300 gtaatagttc tggaactaaa gatggctggg cagtgctccc aaaatgaata ttttgacagt 360 ttgttgcatg cttgcatacc ttgtcaactt cgatgttctt ctaatactcc tcctctaaca 420 tgtcagcgtt attgtaatgc aagtgtgacc aattcagtga aaggaacgaa tgcgattctc 480 tggacctgtt tgggactgag cttaataatt tctttggcag ttttcgtgct aatgtttttg 540

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<211> 34
<212> PRT
<213> Homo sapiens
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Glu Leu Glu Lys Ser Lys Arg Ala Leu Glu Thr Gln Met Glu Glu Met
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Lys Thr
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<212> DNA
<213> Homo sapiens
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104/299

Leu Leu Glu Glu Glu Thr Arg Gln Lys Leu Asn Val Ser 20 25

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<211> 89

<212> DNA

<213> Homo sapiens

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<210> 132

<211> 452

<212> PRT

<213> Homo sapiens

<400> 132

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Tyr Thr Pro Pro Glu Ser Pro Val Pro Ser Tyr Ala Ser Ser Thr Pro
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Leu His Val Pro Val Pro Arg Ala Leu Arg Met Glu Glu Asp Ser Ile 35 40 45

Arg Leu Pro Ala His Leu Arg Leu Gln Pro Ile Tyr Trp Ser Arg Asp 50 55 60

Asp Val Ala Gln Trp Leu Lys Trp Ala Glu Asn Glu Phe Ser Leu Arg 65 70 75 80

Pro Ile Asp Ser Asn Thr Phe Glu Met Asn Gly Lys Ala Leu Leu Leu 85 90 95

Leu Thr Lys Glu Asp Phe Arg Tyr Arg Ser Pro His Ser Gly Asp Val
100 105 110

Leu Tyr Glu Leu Leu Gln His Ile Leu Lys Gln Arg Lys Pro Arg Ile 115 120 125

Leu Phe Ser Pro Phe Phe His Pro Gly Asn Ser Ile His Thr Gln Pro 130 135 140

Glu Val Ile Leu His Gln Asn His Glu Glu Asp Asn Cys Val Gln Arg 145 150 155 160

Thr Pro Arg Pro Ser Val Asp Asn Val His His Asn Pro Pro Thr Ile 165 170 175

Glu Leu Leu His Arg Ser Arg Ser Pro Ile Thr Thr Asn His Arg Pro 180 185 190

Ser Pro Asp Pro Glu Gln Arg Pro Leu Arg Ser Pro Leu Asp Asn Met

105/299

195 200 205

Ile Arg Arg Leu Ser Pro Ala Glu Arg Ala Gln Gly Pro Arg Pro His 210 215 220

Gln Glu Asn Asn His Gln Glu Ser Tyr Pro Leu Ser Val Ser Pro Met 225 230 235

Glu Asn Asn His Cys Pro Ala Ser Ser Glu Ser His Pro Lys Pro Ser 245 250 255

Ser Pro Arg Gln Glu Ser Thr Arg Val Ile Gln Leu Met Pro Ser Pro 260 265 270

Ile Met His Pro Leu Ile Leu Asn Pro Arg His Ser Val Asp Phe Lys 275 280 285

Gln Ser Arg Leu Ser Glu Asp Gly Leu His Arg Glu Gly Lys Pro Ile 290 295 300

Asn Leu Ser His Arg Glu Asp Leu Ala Tyr Met Asn His Ile Met Val 305 310 315

Ser Val Ser Pro Pro Glu Glu His Ala Met Pro Ile Gly Arg Ile Ala 325 330 335

Asp Cys Arg Leu Leu Trp Asp Tyr Val Tyr Gln Leu Leu Ser Asp Ser 340 345 350

Arg Tyr Glu Asn Phe Ile Arg Trp Glu Asp Lys Glu Ser Lys Ile Phe 355 360 365

Arg Ile Val Asp Pro Asn Gly Leu Ala Arg Leu Trp Gly Asn His Lys 370 375 380

Asn Arg Thr Asn Met Thr Tyr Glu Lys Met Ser Arg Ala Leu Arg His 385 390 395 400

Tyr Tyr Lys Leu Asn Ile Ile Arg Lys Glu Pro Gly Gln Arg Leu Leu 405 410 415

Phe Arg Phe Met Lys Thr Pro Asp Glu Ile Met Ser Gly Arg Thr Asp 420 425 430

Arg Leu Glu His Leu Glu Ser Gln Glu Leu Asp Glu Gln Ile Tyr Gln 435 440 445

Glu Asp Glu Cys 450

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<211> 1956

<212> DNA

<213> Homo sapiens

<400> 133

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<210> 134

<211> 452

<212> PRT

<213> Homo sapiens

<400> 134

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Leu His Val Pro Val Pro Arg Ala Leu Arg Met Glu Glu Asp Ser Ile 35 40 45

Arg Leu Pro Ala His Leu Arg Leu Gln Pro Ile Tyr Trp Ser Arg Asp
50 55 60

Asp Val Ala Gln Trp Leu Lys Trp Ala Glu Asn Glu Phe Ser Leu Arg 65 70 75 80

Pro Ile Asp Ser Asn Thr Phe Glu Met Asn Gly Lys Ala Leu Leu Leu 85 90

107/299

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109/299
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#### 112/299

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Ala Lys Lys Pro Thr Ala Ala Glu Val Ser Val Arg Val Pro Arg Gly
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Pro Pro Ser Glu Leu His Lys Val His Gly Ser Arg Asn Lys Pro Thr 545 550 555 560

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115/299

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118/299

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Ile Gln Thr Ala Glu Gly Ser Pro Lys Gln Val Phe Pro Ser Leu Lys
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Glu Leu Ile Ser Lys Phe Glu Lys Pro Asn Gln Gly Met Val Val His
85 90 95

Leu Leu Lys Pro Ile Lys Arg Thr Ser Pro Ser Leu Arg Trp Arg Gly
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Asp Val Leu Pro 130

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119/299

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<213> Mus musculus

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Leu Val Tyr Ser Tyr Arg Ile Phe Arg Glu Lys His Gly Tyr Tyr Arg
50 60

Ile Glu Thr Asp Ala His Thr Pro Arg Thr Ile Phe Pro Asn Leu Gln 65 70 75 80

Glu Leu Val Ser Lys Tyr Gly Lys Pro Gly Gln Gly Leu Val Val His \$90\$

Leu Ser Asn Pro Ile Met Arg Asn Asn Leu Cys Gln Arg Gly Arg Arg 100 105 110

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Asp Val Leu Pro 130

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Ile Gln Leu Trp Gln Phe Leu Leu Glu Leu Leu Ser Asp Ser Ala Asn
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Glu 225	Ala	Glu	Thr	Arg	Ile 230	Leu	Gln	Glu	ГÀЗ	Leu 235	Asp	Gln	Pro	Val	Ser 240
Ala	Pro	Pro	Ser	Pro 245	Arg	Asp	Ile	Ser	Met 250	Glu	Ile	Asp	Ser	Pro 255	Glu
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Gln	Tyr 290	Leu	Glu	Glu	Glu	Arg 295	His	Met	Arg	Glu	Glu 300	Asn	Leu	Arg	Leu
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Gln	His	Met	Gly	Thr 405	Ser	His	Gly	Ile	Thr 410	Arg	Pro	Ser	Pro	Arg 415	Arg
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Asn Thr Gln Thr Pro Val Gln Pro Pro Pro Pro Pro Pro Pro Pro 440 435 Met Gln Pro Thr Val Pro Ser Gly Ser His Leu Ala Ala Tyr Ser Phe 455 Ala Thr Phe Gly Ala His Leu Leu Pro Ala Leu Met His Glu Leu Ser 465 470 475 Leu Asn Phe Lys Leu Gly Leu Ile Gln Trp Ser Arg Leu Leu Asn Ala 490 Lys Gly Ser Phe Ser Gly Ile Phe Gly Tyr Asp Leu Phe Ala Leu Arg Leu Ser Arg Leu His Tyr Pro Leu Cys Cys Lys Cys Leu Ser Glu Met 520 Gln Pro Val Leu Trp Val Tyr Asn Thr Asn Gln Thr Thr Phe Ser Ile 535 Ser Val Leu Leu Glu Ser Ser Cys Thr Ser Ile Pro Trp Leu Glu Pro 550 555 Ser Leu Phe Gly Ile Trp Tyr Phe Ser Ser Ser Val Gln Phe Leu Leu 565 570 Gly Pro Glu Leu His Ser Pro Gly Phe 580 <210> 163 <211> 3011 <212> DNA <213> Homo sapiens <400> 163

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125/299

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126/299

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		128/299		
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Gly Ser Ser 50	Gln Lys Ala	His Gly Ile Leu A	la Arg Arg Pro Ser 60	Tyr
Arg Lys Ile 65	Leu Lys Asp 70		sp Thr Arg Gly Arg 75	Lys 80
Gly Asp Gly	Glu Asn Ser 85	Gly Val Ser Ala A	la Val Thr Ser Met 95	Ser
Val Pro Thr	Pro Ile Tyr 100	Gln Thr Ser Ser G	ly Gln Tyr Ile Ala 110	Ile

Ala Pro Asn Gly Ala Leu Gln Leu Ala Ser Pro Gly Thr Asp Gly Val

Gln Gly Leu Gln Thr Leu Thr Met Thr Asn Ser Gly Ser Thr Gln Gln

Gly Thr Thr Ile Leu Gln Tyr Ala Gln Thr Ser Asp Gly Gln Gln Ile

Leu Val Pro Ser Asn Gln Val Val Gln Thr Ala Ser Gly Asp Met

Gln Thr Tyr Gln Ile Arg Thr Thr Pro Ser Ala Thr Ser Leu Pro Gln 180 185 190

170

115 120

1.35

129/299

Thr Val Val Met Thr Ser Pro Val Thr Leu Thr Ser Gln Thr Thr Lys 195 200 Thr Asp Asp Pro Gln Leu Lys Arg Glu Ile Arg Leu Met Lys Asn Arg 215 Glu Ala Ala Arg Glu Cys Arg Arg Lys Lys Glu Tyr Val Lys Cys Leu Glu Asn Arg Val Ala Val Leu Glu Asn Gln Asn Lys Thr Leu Ile Glu Glu Leu Lys Thr Leu Lys Asp Leu Tyr Ser Asn Lys Ser Val 265 <210> 169 <211> 816 <212> DNA <213> Homo sapiens <400> 169 atggaagatt cccacaagag taccacgtca gagacagcac ctcaacctgg ttcagcagtt 60 cagggagctc acatttctca tattgctcaa caggtatcat ctttatcaga aagtgaggag 120 teccaggact cateegacag cataggetee teacagaaag cecaegggat cetageacgg 180 cgcccatctt acagaaaaat tttgaaagac ttatcttctg aagatacacg qqqcaqaaaa 240 ggagacggag aaaattctgg agtttctgct gctgtcactt ctatqtctgt tccaactccc 300 atctatcaga ctagcagcgg acagtacatt gccattgccc caaatggagc cttacagttg 360 gcaagtccag gcacagatgg agtacaggga cttcagacat taaccatgac aaattcaggc 420 agtactcagc aaggtacaac tattcttcag tatgcacaga cctctgatgg acagcagata 480 cttgtgccca gcaatcaggt ggtcgtacaa actgcatcag gagatatgca aacatatcag 540 atocgaacta caccttcagc tacttctctq ccacaaactg tqqtqatgac atotcctqtq 600 acteteacet eteagacaac taagacagat gacceecaat tqaaaagaga aataaqqtta 660 atqaaaaaca qaqaaqctqc tcqaqaatqt cqcaqaaaqa aqaaaqaata tqtqaaatqc 720 ctggaaaacc gagttgcagt cctggaaaat caaaataaaa ctctaataga agagttaaaa 780 actttgaagg atctttattc caataaaagt gtttga <210> 170 <211> 117 <212> PRT <213> Homo sapiens <400> 170 Thr Gly Ser Tyr Ser Gln Ala Pro Ser Gln Tyr Ser Gln Gln Ser Ser 1.0 Ser Tyr Gly Gln Gln Ile Ala Ile Ala Pro Asn Gly Ala Leu Gln Leu Ala Ser Pro Gly Thr Asp Gly Val Gln Gly Leu Gln Thr Leu Thr Met Thr Asn Ser Gly Ser Thr Gln Gln Gly Thr Thr Ile Leu Gln Tyr Ala Gln Thr Ser Asp Gly Gln Gln Ile Leu Val Pro Ser Asn Gln Val Val 65 70 75

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131/299

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Gly Gln Gln Asp Arg Gly Gly Arg Gly Gly Gly Ser Gly Gly Gly

220

215

210

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Ser	Asp	Arg	Gly 260	Gly	Phe	Asn	ГЛЗ	Phe 265	Gly	Gly	Pro	Arg	Asp 270	Gln	Gly
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Ala	Pro 450	Lys	Pro	Asp	Gly	Pro 455	Gly	Gly	Gly	Pro	Gly 460	Gly	Ser	His	Met
Gly 465	Gly	Asn	Tyr	Gly	Asp 470	Asp	Arg	Arg	Gly	Gly 475	Arg	Gly	Gly	Tyr	Asp 480
Arg	Gly	Gly	Tyr	Arg 485	Gly	Arg	Gly	Gly	Asp 490	Arg	Gly	Gly	Phe	Arg 495	Gly
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Gln Pro Ser Tyr Gly Gly Gln Gln Ser Tyr Gly Gln Gln Gln Ser
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135/299

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137/299

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#### 138/299

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Gly Tyr Gly Gln Ser Ser Tyr Ser Ser Tyr Gly Gln Ser Gln Asn Ser 50 55 60

Tyr Gly Thr Gln Ser Thr Pro Gln Gly Tyr Gly Ser Thr Gly Gly Tyr 65 70 75 80

Gly Ser Ser Gln Ser Ser Gln Ser Ser Tyr Gly Gln Gln Ser Ser Tyr
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Pro Gly Tyr Gly Gln Gln Pro Ala Pro Ser Ser Thr Ser Gly Ser Tyr 100 . 105 110

Gly Ser Ser Ser Gln Ser Ser Ser Tyr Gly Gln Pro Gln Ser Gly Ser 115 120 125

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Asn Ser Ser Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Asn Tyr \$165\$ \$170\$

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139/299

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#### 141/299

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142/299

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146/299

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152/299

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156/299

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158/299

Phe Her Try Cys Try Asn Thr Sel Val Glu Asn Sel Val Glu Asn His Sel Leu Arg His Wal Ala Arg Arg Lys Ala Glu Arg His Wal Arg Arg Arg Lys Ala Glu Pro Glu Gly Leu Arg Arg Arg Lys Ala Ile Met Thr Phe Lys Asp Tyr 130 Try Cys Try Asn Thr Phe Val Glu Asn Ser Val Arg Leu Ser Arg Gln Leu Arg Gln Leu Arg Arg Lys Ala Try Glu Gly Leu His Glu Asn Ser Val Arg Leu Ser Arg Gln Leu

165 170 175

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Phe Arg Thr Leu Gly Leu 195

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		•	
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Thr Gln Ser Ser Ser 20	Ser Glu Glu Ile Va 25	al Pro Ser Pro Pro 30	
Pro Pro Leu Pro Arg 35	Ile Tyr Lys Pro Cy	ys Phe Val Cys Glr 45	n Asp Lys
Ser Ser Gly Tyr His	Tyr Gly Val Ser Al	la Cys Glu Gly Cys 60	E Lys Gly
Phe Phe Arg Arg Ser 65	Ile Gln Lys Asn Me	et Val Tyr Thr Cys 75	s His Arg 80
Asp Lys Asn Cys Ile 85		nr Arg Asn Arg Cys 90	Gln Tyr 95
Cys Arg Leu Gln Lys 100	Cys Phe Glu Val G	ly Met Ser Lys Gli 110	
Arg Asn Asp Arg Asn 115	Lys Lys Lys G	lu Val Pro Lys Pro 125	o Glu Cys
Ser Glu Ser Tyr Thr 130	Leu Thr Pro Glu Va	al Gly Glu Leu Ile 140	e Glu Lys .
Val Arg Lys Ala His 145	Gln Glu Thr Phe Pr	co Ala Leu Cys Glr 155	n Leu Gly 160

160/299

Lys Tyr Thr Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile 165 170 175

Asp Leu Trp Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys
180 185 190

Thr Val Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile 195 200 205

Ala Asp Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile 210 215 220

Leu Arg Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe 225 230 235 240

Ser Asp Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe 245 250 255

Gly Pro Leu Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro 260 265 270

Leu Glu Met Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu 275 280 285

Ile Cys Gly Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met 290 295 300

Leu Gln Glu Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg 305 310 315 320

Arg Pro Ser Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr
325 330 335

Asp Leu Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu 340 345 350

Lys Met Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu 355 360 365

Glu Asn Ser Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly 370 375 380

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Arg Gln Pro		er Pro Ser 40	Pro Thr Glu	ı Arg Ala Pro 45	o Ala Ser			
Glu Glu Gl <sup>.</sup> 50	u Phe Gln P	he Leu Arg 55	Cys Gln Glr	Cys Gln Ala 60	a Glu Ala			
Lys Cys Pro 65	_	eu Pro Cys 70	Leu His Thr	Leu Cys Se	r Gly Cys 80			
Leu Glu Al	a Ser Gly M 85	et Gln Cys	Pro Ile Cys 90	Gln Ala Pro	o Trp Pro 95			
Leu Gly Ala	a Asp Thr P 100	ro Ala Leu	Asp Asn Val	. Phe Phe Gli 11				
Gln Arg Arg		al Tyr Arg 120	Gln Ile Val	Asp Ala Gli 125	n Ala Val			
Cys Thr Ar	g Cys Lys G	lu Ser Ala 135	Asp Phe Tr	Cys Phe Gl	ı Cys Glu			
Gln Leu Le	_	ys Cys Phe 50	Glu Ala His 155	Gln Trp Pho	e Leu Lys 160			
773 m (77. m.)	n Aren Dres T	715 G1	T 7 7		1 7 07			

His Glu Ala Arg Pro Leu Ala Glu Leu Arg Asn Gln Ser Val Arg Glu

162/299

165 170 175 Phe Leu Asp Gly Thr Arg Lys Thr Asn Asn Ile Phe Cys Ser Asn Pro 185 Asn His Arg Thr Pro Thr Leu Thr Ser Ile Tyr Cys Arg Gly Cys Ser 200 Lys Pro Leu Cys Cys Ser Cys Ala Leu Leu Asp Ser Ser His Ser Glu 215 Leu Lys Cys Asp Ile Ser Ala Glu Ile Gln Gln Arg Gln Glu Glu Leu 230 Asp Ala Met Thr Gln Ala Leu Gln Glu Gln Asp Ser Ala Phe Gly Ala 250 Val His Ala Gln Met His Ala Ala Val Gly Gln Leu Gly Arg Ala Arg Ala Glu Thr Glu Glu Leu Ile Arg Glu Arg Val Arg Gln Val Val Ala 280 His Val Arg Ala Gln Glu Arg Glu Leu Leu Glu Ala Val Asp Ala Arg Tyr Gln Arg Asp Tyr Glu Glu Met Ala Ser Arg Leu Gly Arg Leu Asp 310 Ala Val Leu Gln Arg Ile Arg Thr Gly Ser Ala Leu Val Gln Arg Met 325 330 Lys Cys Tyr Ala Ser Asp Gln Glu Val Leu Asp Met His Gly Phe Leu 345 Arg Gln Ala Leu Cys Arg Leu Arg Gln Glu Glu Pro Gln Ser Leu Gln 360 Ala Ala Val Arg Thr Asp Gly Phe Asp Glu Phe Lys Val Arg Leu Gln 375 Asp Leu Ser Ser Cys Ile Thr Gln Gly Lys Ala Ile Glu Thr Gln Ser 390 Ser Ser Ser Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro Leu Pro Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg Leu 470

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Arg	Asn	Lуs	Lys 500	Lys	Ьуs	Glu	Val	Pro 505	Lys	Pro	Glu	Cys	Ser 510	Glu	Ser
Tyr	Thr	Leu 515	Thr	Pro	Glu	Val	Gly 520	Glu	Leu	Ile	Glu	Lys 525	Val	Arg	Ъуз
Ala	His 530	Gln	Glu	Thr	Phe	Pro 535	Ala	Leu	Cys	Gln	Leu 540	Gly	Lys	Tyr	Thr
Thr 545	Asn	Asn	Ser	Ser	Glu 550	Gln	Arg	Val	Ser	Leu 555	Asp	Ile	Asp	Leu	Trp 560
Asp	Lys	Phe	Ser	Glu 565	Leu	Ser	Thr	Lys	Cys 570	Ile	Ile	Lys	Thr	Val 575	Glu
Phe	Ala	Lys	Gln 580	Leu	Pro	Gly	Phe	Thr 585	Thr	Leu	Thr	Ile	Ala 590	Asp	Gln
Ile	Thr	Leu 595	Leu	Lys	Ala	Ala	Сув 600	Leu	Asp	Ile	Leu	Ile 605	Leu	Arg	Ile
Сув	Thr 610	Arg	Tyr	Thr	Pro	Glu 615	Gln	Asp	Thr	Met	Thr 620	Phe	Ser	Asp	Gly
Leu 625	Thr	Leu	Asn	Arg	Thr 630	Gln	Met	His	Asn	Ala 635	Gly	Phe	Gly	Pro	Leu 640
Thr	Asp	Leu	Val	Phe 645	Ala	Phe	Ala	Asn	Gln 650	Leu	Leu	Pro	Leu	Glu 655	Met
Asp	Asp	Ala	Glu 660	Thr	Gly	Leu	Leu	Ser 665	Ala	Ile	Cys	Leu	Ile 670	Cys	Gly
Asp	Arg	Gln 675	Asp	Leu	Glu	Gln	Pro 680	Asp	Arg	Val	Asp	Met 685	Leu	Gln	Glu
Pro	Leu 690	Leu	Glu	Ala	Leu	Lys 695	Val	Tyr	Val-	Arg	Lys 700	Arg	Arg	Pro	Ser
Arg 705	Pro	His	Met	Phe	Pro 710	Lys	Met	Leu	Met	Lys 715	Ile	Thr	Asp	Leu	Arg 720
Ser	Ile	Ser	Ala	Lys 725	Gly	Ala	Glu	Arg	Val 730	Ile	Thr	Leu	Lys	Met 735	Glu
Ile	Pro	Gly	Ser 740	Met	Pro	Pro	Leu	Ile 745	Gln	Glu	Met	Leu	Glu 750	Asn	Ser
Glu	Gly	Leu 755	Asp	Thr	Leu	Ser	Gly 760	Gln	Pro	Gly	Gly	Gly 765	Gly	Arg	Asp
Gly	Gly 770	Gly	Leu	Ala	Pro	Pro 7 <b>7</b> 5	Pro	Gly	Ser	Сув	Ser 780	Pro	Ser	Leu ·	Ser

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35 40 45

Thr Pro Leu Trp Asn Gly Ser Asn His Ser Ile Glu Thr Gln Ser Ser 50 60

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Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser Gly Tyr 85 90 95

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Leu Cys Asp Val Val Ile Met Val Asp Ser Gln Glu Phe His Ala His

166/299

35 40 Arg Thr Val Leu Ala Cys Thr Ser Lys Met Phe Glu Ile Leu Phe His 55 Arg Asn Ser Gln His Tyr Thr Leu Asp Phe Leu Ser Pro Lys Thr Phe Gln Gln Ile Leu Glu Tyr Ala Tyr Thr Ala Thr Leu Gln Ala Lys Ala Glu Asp Leu Asp Asp Leu Leu Tyr Ala Ala Glu Ile Leu Glu Ile Glu Tyr Leu Glu Glu Gln Cys Leu Lys Met Leu Glu Thr Ile Gln Ala Ser 120 Asp Asp Asn Asp Thr Glu Ala Thr Met Ala Asp Gly Gly Ala Glu Glu 135 Glu Glu Asp Arg Lys Ala Arg Tyr Leu Lys Asn Ile Phe Ile Ser Lys 150 155 His Ser Ser Glu Glu Ser Gly Tyr Ala Ser Val Ala Gly Gln Ser Leu 165 Pro Gly Pro Met Val Asp Gln Ser Pro Ser Val Ser Thr Ser Phe Gly Leu Ser Ala Met Ser Pro Thr Lys Ala Ala Val Asp Ser Leu Met Thr Ile Gly Gln Ser Leu Leu Gln Gly Thr Leu Gln Pro Pro Ala Gly Pro Glu Glu Pro Thr Leu Ala Gly Gly Gly Arg His Pro Gly Val Ala Glu Val Lys Thr Glu Met Met Gln Val Asp Glu Val Pro Ser Gln Asp Ser 250 Pro Gly Ala Ala Glu Ser Ser Ile Ser Gly Gly Met Gly Asp Lys Val 265 Glu Glu Arg Gly Lys Glu Gly Pro Gly Thr Pro Thr Arg Ser Ser Val 280 Ile Thr Ser Ala Arg Glu Leu His Tyr Gly Arg Glu Glu Ser Ala Glu Gln Val Pro Pro Pro Ala Glu Ala Gly Gln Ala Pro Thr Gly Arg Pro Glu His Pro Ala Pro Pro Pro Glu Lys His Leu Gly Ile Tyr Ser Val 325 Leu Pro Asn His Lys Ala Asp Ala Val Leu Ser Met Pro Ser Ser Val 340 345

Thr	Ser	Gly 355	Leu	His	Val	Gln	Pro 360	Ala	Leu	Ala	Val	Ser 365	Met	Asp	Phe
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Phe 385	Ser	Lys	Leu	Gly	Glu 390	Leu	Ala	Val	Gly	Met 395	Lys	Ser	Glu	Ser	Arg 400
Thr	Ile	Gly	Glu	Gln 405	Сув	Ser	Val	Cys	Gly 410	Val	Glu	Leu	Pro	Asp 415	Asn
Glu	Ala	Val	Glu 420	Gln	His	Arg	ГÀв	Leu 425	His	Ser	Gly	Met	Lуs 430	Thr	Tyr
Gly	Cys	Glu 435	Leu	Cys	Gly	Lys	Arg 440	Phe	Leu	Asp	Ser	Leu 445	Arg	Leu	Arg
Met	His 450	Leu	Leu	Ala	His	Ser 455	Ala	Gly	Ala	Lys	Ala 460	Phe	Val	Cys	Asp
Gln 465	Cys	Gly	Ala	Gln	Phe 470	Ser	Lys	Glu	qaA	Ala 475	Leu	Glu	Thr	His	Arg 480
Gln	Thr	His	Thr	Gly 485	Thr	Asp	Met	Ala	Val 490	Phe	Cys	Leu	Leu	Cys 495	Gly
Lys	Arg	Phe	Gln 500	Ala	Gln	Ser	Ala	Leu 505	Gln	Gln	His	Met	Glu 510	Val	His
Ala	Gly	Val 515	Arg	Ser	Tyr	Ile	Cys 520	Ser	Glu	Сув	Asn	Arg 525	Thr	Phe	Pro
Ser	His 530	Thr	Ala	Leu	Lys	Arg 535	His	Leu	Arg	Ser	His 540	Thr	Gly	Asp	His
Pro 545	Tyr	Glu	Сув	Glu	Phe 550	Сув	Gly	Ser	Cys	Phe 555	Arg	Asp	Glu	Ser	Thr 560
Leu	Lys	Ser	His	Ъув 565	Arg	Ile	His	Thr	Gly 570	Glu	Lys	Pro	Tyr	Glu 575	Cys
Asn	Gly	Cys	Asp 580	Lys	Lys	Phe	Ser	Leu 585	Lys	His	Gln	Leu	Glu 590	Thr	His
Tyr	Arg	Val 595	His	Thr	Gly	Glu	Lys 600	Pro	Phe	Glu	Сув	Lуs 605	Leu	Cys	His
Gln	Arg 610	Ser	Arg	Asp	Tyr	Ser 615	Ala	Met	Ile	Lys	His 620	Leu	Arg	Thr	His
Asn 625	Gly	Ala	Ser	Pro	Tyr 630	Gln	Cys	Thr	Ile	Сув 635	Thr	Glu	Tyr	Cys	Pro 640
Ser	Leu	Ser	Ser	Met 645	Gln	Lys	His	Met	Lys 650	Gly	His	Lys	Pro	Glu 655	Glu

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Leu	Cys	Asp 35	Val	Val	Ile	Met	Val 40	Asp	Ser	Gln	Glu	Phe 45	His	Ala	His
Arg	Thr 50	Val	Leu	Ala	Cys	Thr 55	Ser	Lys	Met	Phe	Glu 60	Ile	Leu	Phe	His
Arg 65	Asn	Ser	Gln	His	Tyr 70	Thr	Leu	Asp	Phe	Leu 75	Ser	Pro	Lys	Thr	Phe 80
Gln	Gln	Ile	Leu	Glu 85	Tyr	Ala	Tyr	Thr	Ala 90	Thr	Leu	Gln	Ala	Lys 95	Ala
Glu	Asp	Leu	Asp 100	Asp	Leu	Leu	Tyr ·	Ala 105	Ala	Glu	Ile	Leu	Glu 110	Ile	Glu
Tyr	Leu	Glu 115	Glu	Gln	Cys	Leu	Lys 120	Met	Leu	Glu	Thr	Ile 125	Gln	Ala	Ser
Asp	Asp 130	Asn	Asp	Thr	Glu	Ala 135	Thr	Met	Ala	Asp	Gly 140	Gly	Ala	Glu	Glu
Glu 145	Glu	Asp	Arg	Lys	Ala 150	Arg	Tyr	Leu	Lys	Asn 155	Ile	Phe	Ile	Ser	Lys 160
His	Ser	Ser	Glu	Glu 165	Ser	Gly	Tyr	Ala	Ser 170	Val	Ala	Gly	Gln	Ser 175	Leu
Pro	Gly	Pro	Met 180	Val	Asp	Gln	Ser	Pro 185	Ser	Val	Ser	Thr	Ser 190	Phe	Gly
Leu	Ser	Ala 195	Met	Ser	Pro	Thr	Lys 200	Ala	Ala	Val	Asp	Ser 205	Leu	Met	Thr
Ile	Gly 210	Gln	Ser	Leu	Leu	Gln 215	Gly	Thr	Leu	Gln	Pro 220	Pro	Ala	Gly	Pro
Glu 225	Glu	Pro	Thr	Leu	Ala 230	Gly	Gly	Gly	Arg	His 235	Pro	Gly	Val	Ala	Glu 240
Val	Lys	Thr	Glu	Met 245	Met	Gln	Val	Asp	Glu 250	Val	Pro	Ser	Gln	Asp 255	Ser
Pro	Gly	Ala	Ala 260	Glu	Ser	Ser	Ile	Ser 265	Gly	Gly	Met	Gly	Asp 270	Lys	Val
Glu	Glu	Arg 275	Gly	Lys	Glu	Gly	Pro 280	Gly	Thr	Pro	Thr	Arg 285	Ser	Ser	Val.
Ile	Thr 290	Ser	Ala	Arg	Glu	Leu 295	His	Tyr	Gly	Arg	Glu 300	Glu	Ser	Ala	Glu
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# 170/299

Glu His Pro Ala Pro Pro Pro Glu Lys His Leu Gly Ile Tyr Ser Val 330 Leu Pro Asn His Lys Ala Asp Ala Val Leu Ser Met Pro Ser Ser Val 345 Thr Ser Gly Leu His Val Gln Pro Ala Leu Ala Val Ser Met Asp Phe 355 Ser Thr Tyr Gly Gly Leu Leu Pro Gln Gly Phe Ile Gln Arg Glu Leu Phe Ser Lys Leu Gly Glu Leu Ala Val Gly Met Lys Ser Glu Ser Arg Thr Ile Gly Glu Gln Cys Ser Val Cys Gly Val Glu Leu Pro Asp Asn 410 Glu Ala Val Glu Gln His Arg Lys Leu His Ser Gly Met Lys Thr Tyr Gly Cys Glu Leu Cys Gly Lys Arg Phe Leu Asp Ser Leu Arg Leu Arg Met His Leu Leu Ala His Ser Ala Gly Ala Lys Ala Phe Val Cys Asp 450 455 Gln Cys Gly Ala Gln Phe Ser Lys Glu Asp Ala Leu Glu Thr His Arg 475 Gln Thr His Thr Gly Thr Asp Met Ala Val Phe Cys Leu Leu Cys Gly 485 490 Lys Arg Phe Gln Ala Gln Ser Ala Leu Gln Gln His Met Glu Val His 505 Ala Gly Val Arg Ser Tyr Ile Cys Ser Glu Cys Asn Arg Thr Phe Pro Ser His Thr Ala Leu Lys Arg His Leu Arg Ser His Thr Gly Asp His Pro Tyr Glu Cys Glu Phe Cys Gly Ser Cys Phe Arg Asp Glu Ser Thr Leu Lys Ser His Lys Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys 570 Asn Gly Cys Asp Lys Lys Phe Ser Leu Lys His Gln Leu Glu Thr His Tyr Arg Val His Thr Gly Glu Lys Pro Phe Glu Cys Lys Leu Cys His Gln Arg Ser Arg Asp Tyr Ser Ala Met Ile Lys His Leu Arg Thr His 615

171/299

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Asn Gly Ala Ser Pro Tyr Gln Cys Thr Ile Cys Thr Glu Tyr Cys Pro
625
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                                        635
Ser Leu Ser Ser Met Gln Lys His Met Lys Gly His Lys Pro Glu Glu
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Ile Pro Pro Asp Trp Arg Ile Glu Lys Thr Tyr Leu Tyr Leu Cys Tyr
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Val
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172/299

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Gln Glu
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taccataagg ggtttaaata ggaatgtttt ctccaaagtg aatcttgaaa tcttggtgtt 180
tataattgtc aagcctcttt ttttaaaata gatttggtca acaggaagta tttttttcta 240
attitutatti tatagaccta gicaagctic tiaatigita aatatigita taacaataca 300
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178/299

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Thr His Thr Asp Val Ser Ser Phe Gln Thr Met Asp Gln Met Val Ser 65 70 75 80

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Ser Val Asp Pro Asn Gly His Ser Phe Cys Ser Ser Ser Val Met Thr
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Tyr Ser Lys Ile Gly Asp Glu Pro Pro Lys Val Phe Gln Ala Ser Thr 115 120 125

Gln Thr Arg Arg Ala Pro Gly Gly Ile Lys Glu Thr Arg Lys Ala Met 130 135 140

Arg Asp Ser Asp Ser Gly Leu Glu Lys Met Ala Ile Gly His His Ile
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His Asp Arg Ala His Val Ile Lys Lys Ser Lys Asn Lys Lys Thr Gly
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Asn Pro Gly Ser Arg Glu Leu Lys Arg Arg Glu Lys Pro Gln Gln Ser 225 230 235 240

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179/299

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His	Asp	Arg	Ala	His 165	Val	Ile	Lys	Lys	Ser 170	Lys	Asn	Lys	Lys	Thr 175	Gly	
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180/299

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Asp Leu Gly Ser Phe Leu Leu Gly Ser Thr Phe Leu Ser Thr Gly

Thr Thr Leu Pro Phe Ile Thr Ser Val Glu Ile Val Ser Arg Tyr Leu

Cys Ala Arg Gly Ser Gly Arg Ala Gly His His Gly Pro Gly Arg Ala

Arg Pro Ala Val Ala Thr Ser Ala Phe Pro Ala Gln Glu Pro Arg Val

Phe Leu Arg Ser Ala Leu Pro Ala Gly Arg Leu Ser Pro Ser Thr Thr 105

His Leu His Leu Val Thr Ala Asp Asn Pro Ala Ala Asn Trp Leu His 120

Ala Arg Ser Thr Arg Lys Lys Arg Cys Pro Tyr Thr Lys His Gln Thr 135

Leu Glu Leu Glu Lys Glu Phe Leu Phe Asn Met Tyr Leu Thr Arg Asp 145 150 155

182/299

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His Leu His Leu Val Thr Ala Asp Asn Pro Ala Ala Asn Trp Leu His 115 120 125

183/299

Ala Arg Ser Thr Arg Lys Lys Arg Cys Pro Tyr Thr Lys His Gln Thr 130 140

Leu Glu Leu Glu Lys Glu Phe Leu Phe Asn Met Tyr Leu Thr Arg Asp 145 150 155 160

Arg Arg Tyr Glu Val Ala Arg Leu Leu Asn Leu Thr Glu Arg Gln Val
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His His His His His Pro Tyr Val His Pro Gln Ala Pro Trp Arg 85 90 95

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Gly Ala Leu Ser Phe Ala Gly Leu Pro Ser Ser Arg Pro Tyr Gly Ile 115 120 125

Lys Pro Glu Pro Leu Ser Ala Arg Arg Gly Asp Cys Pro Thr Leu Asp 130 135 140

Thr His Thr Phe Ser Leu Thr Asp Tyr Ala Cys Gly Ser Pro Pro Val

Asp Arg Glu Lys Gln Pro Ser Glu Gly Ala Phe Ser Glu Asn Asn Ala 165 170 175

Glu Asn Glu Ser Gly Gly Asp Lys Pro Pro Ile Asp Pro Asn Asn Pro 180 185 190

184/299 Ala Ala Asn Trp Leu His Ala Arg Ser Thr Arg Lys Lys Arg Cys Pro 200 Tyr Thr Lys His Gln Thr Leu Glu Leu Glu Lys Glu Phe Leu Phe Asn 215 Met Tyr Leu Thr Arg Asp Arg Tyr Glu Val Ala Arg Leu Leu Asn 225 230 Leu Thr Glu Arg Gln Val Lys Ile Trp Phe Gln Asn Arg Arg Met Lys 245 250 255 Met Lys Lys Ile Asn Lys Asp Arg Ala Lys Asp Glu <210> 243 <211> 6671 <212> DNA <213> Homo sapiens <400> 243 egtteteete tettteteet eteeteetgg aatacettae tgggeetggt ggetteeett 60 cttgaccatt tgcggccct ggggcactct gttgcactgg cgggcgcagg ttcctagggg 120 ctgggctggg ccgggccagg cgcgatggca gggttctctc cttggcggcg gcggcagcgg 180 cggaggeggc ggeggggg ggcgaggcac gcttcgcggg cagcaccaga actggtcggt 240 gatttaggta gtttcctgtt gttgggatcc acctttctct cgacaggcac gacactgccc 300 ttcattactt cagttgaaat cgtctccagg tacctctgcg cgcgggggtc gggccgcgcg 360 gggcatcacg gccctggtcg tgccaggcct gcggtggcaa cctcggcttt ccctgctcag 420 gagectegtg tettteteeg cagegetttg ccageeggee ggettteeec ttecaccaca 480 cacctccacc tggtcacagc aggtagggtt aggttggctg ctccttcgcg gacgccgggg 540 gegtggtagg aattetggge tttgggeatt caaggteagg ggegeeeget tecateetga 600 gcctcccact ggaggctgcg cctgcccagg gacctcctgc cattctcttg taaggctgga 660 tgageteagg aaagaacete etteeagtgg agaeteagge tggaetagga aggataggge 780 aggetgggat cetggeettg teacttacee ttetetetqt aageteggee getgetagga 840 gtegeetete ttttetteet tetttteeet gtetteeett eetetttat etettette 900 tetteegtet etgecagatt etateteace teettatete etteceaaag cateettggg 1020 gaggggccca gagctggctt caggagagcc tagggggtct cactttcctc tgcggctcaa 1080 gtagaggttg ggaagtetge egaggaaggg ceegegtggg geggetgeeg agggeggtgg 1140 gtttgggcct ggtgtgttac tctgcagaca aggcctcggt tatgatcacg accggatggc 1200 ggcagcettg cgtttetteg cetgtegeta acggetgaet aggagatetg attaggggae 1260 attogotgca gotttgtgtg cocatatoga gggcagggag cottcgccag cotcactggg 1320

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<213> Homo sapiens
<400> 244
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Glu Glu Glu Asp Glu Asn Glu Leu Phe Pro Arg Glu Tyr Phe Arg Arg
Leu Ser Ser Gln Asp Val Leu Arg Cys Gln Ser Ser Ser Lys Arg Lys
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Ser Lys Asp Glu Glu Glu Asp Glu Glu Ser Asp Asp Ala Asp Asp Gly
Asn Asn Trp Glu His Lys Ser Ile Trp Thr Ala Leu
                    70
<210> 245
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gtgtcagtcc tcttctaaqa ggaagtctaa aqatqaaqaa qaaqatqaag agtcaqatqa 180
tgctgatgat gggaataact gggaacacaa gtccatttgg acagcccttt agtcaagctg 240
gagggcagcc aatgggagcc actggagtga acccccagtt agccagcaaa cagagcatgg 300
tcaacagttt gcccaccttc cctacagata tcaagaatac ttcagtcacc aacgtgccaa 360
atatgtctca gatgcaaaca tcagtgggaa ttgtacccac acaagcaatt gcaac
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187/299

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#### 188/299

Ala	Ala	Ser	Lys	His	Lys	${\tt Gln}$	Leu	Ser	Glu	Leu	Leu	Arg	Gly	${\tt Gl}{y}$	Ser
			100					105					110		

- Gly Ser Ser Ile Asn Pro Gly Ile Gly Asn Val Ser Ala Ser Ser Pro 115 120 125
- Val Gln Gln Gly Leu Gly Gln Ala Gln Gly Gln Pro Asn Ser Ala 130 135 140
- Asn Met Ala Ser Leu Ser Ala Met Gly Lys Ser Pro Leu Ser Gln Gly 145 150 155 160
- Asp Ser Ser Ala Pro Ser Leu Pro Lys Gln Ala Ala Ser Thr Ser Gly
  165 170 175
- Pro Thr Pro Ala Ala Ser Gln Ala Leu Asn Pro Gln Ala Gln Lys Gln 180 185 190
- Val Gly Leu Ala Thr Ser Ser Pro Ala Thr Ser Gln Thr Gly Pro Gly 195 200 205
- Ile Cys Met Asn Ala Asn Phe Asn Gln Thr His Pro Gly Leu Leu Asn 210 215 220
- Ser Asn Ser Gly His Ser Leu Ile Asn Gln Ala Ser Gln Gly Gln Ala 225 230 235 240
- Gln Val Met Asn Gly Ser Leu Gly Ala Ala Gly Arg Gly Ala 245 250 255
- Gly Met Pro Tyr Pro Thr Pro Ala Met Gln Gly Ala Ser Ser Val
  260 265 270
- Leu Ala Glu Thr Leu Thr Gln Val Ser Pro Gln Met Thr Gly His Ala 275 280 285
- Gly Leu Asn Thr Ala Gln Ala Gly Gly Met Ala Lys Met Gly Ile Thr 290 295 300
- Gly Asn Thr Ser Pro Phe Gly Gln Pro Phe Ser Gln Ala Gly Gln 305  $$\rm 310$$   $\rm 315$   $\rm 320$
- Pro Met Gly Ala Thr Gly Val Asn Pro Gln Leu Ala Ser Lys Gln Ser 325 330 335
- Met Val Asn Ser Leu Pro Thr Phe Pro Thr Asp Ile Lys Asn Thr Ser 340 345 350
- Val Thr Asn Val Pro Asn Met Ser Gln Met Gln Thr Ser Val Gly Ile 355 360 365
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<211> 1128

<212> DNA

<213> Homo sapiens

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gtgtcagtcc tcttctaaga ggaagtctaa agatgaagaa gaagatgaag agtcagatga 180
tgctgatgat tttggatcat tgtttgactt ggaaaatgat cttcctgatg agctgatacc 240
caatggagga gaattaggcc ttttaaacag tgggaacctt gttccagatg ctgcttccaa 300
acataaacaa ctgtcggagc ttctacgagg aggcagcggc tctagtatca acccaqqaat 360
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gccgaacagt gctaacatgg ccagcctcag tgccatgggc aagagccctc tgagccaggg 480
agattettea gececcagee tgeetaaaca ggeageeage acetetggge ceaccecege 540
tgcctcccaa gcactgaatc cgcaagcaca aaagcaagtg gggctggcga ctagcagccc 600
tgccacgtca cagactggac ctggtatctg catgaatgct aactttaacc aqacccaccc 660
aggcctcctc aatagtaact ctggccatag cttaattaat caggcttcac aagggcaggc 720
gcaagtcatg aatggatete ttggggetge tggcagagga aggggagetg gaatgeegta 780
ccctactcca gccatgcagg gcgcctcgag cagcgtgctg gctgagaccc taacgcaqqt 840
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gccaatggga gccactggag tgaacccca gttagccagc aaacagagca tggtcaacag 1020
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tcagatgcaa acatcagtgg gaattgtacc cacacaagca attgcaac
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<212> PRT
<213> Homo sapiens
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Glu Gln Leu Glu Leu Ser Val Lys Asp Gly Thr Ile Leu Lys Val Ser
Asn Lys Gly Leu Asn Ser Tyr Lys Asp Pro Asp Asn Pro Gly Arg Ile
Ala Leu Pro Lys Pro Arg Asn His Gly Lys Leu Asp Asn Lys Gln Asn
Val Asp Trp Asn Lys Leu Ile Lys Arg Ala Val Glu Gly Leu Ala Glu
                                105
Ser Gly Gly Ser Thr Leu Lys Ser Ile Glu Arg Phe Leu Lys Gly Gln
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Lys Asp Val Ser Ala Leu Phe Gly Gly Ser Ala Ala Ser Gly Phe His
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                        135
Gln Gln Leu Arg Leu Ala Ile Lys Arg Ala Ile Gly His Gly Arg Leu
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Leu	Lys	Asp	Gly	Pro 165	Leu	Tyr	Arg	Leu	Asn 170	Thr	Lys	Ala	Thr	Asn 175	Val
Asp	Gly	Lys	Glu 180	Ser	Cys	Glu	Ser	Leu 185	Ser	Cys	Leu	Pro	Pro 190	Val	Ser
Leu	Leu	Pro 195	His	Glu	Lys	Asp	Lys 200	Pro	Val	Ala	Glu	Pro 205	Ile	Pro	Ile
Суз	Ser 210	Phe	Сув	Leu	Gly	Thr 215	Lys	Glu	Gln	Asn	Arg 220	Glu	Lys	Lys	Pro
Glu 225	Glu	Leu	Ile	Ser	Cys 230	Ala	Asp	Cys	Gly	Asn 235	Ser	Gly	His	Pro	Ser 240
Cys	Leu	Lys	Phe	Ser 245	Pro	Glu	Leu	Thr	Val 250	Arg	Val	ГÀЗ	Ala	Leu 255	Arg
Trp	Gln	Cys	Ile 260	Glu	Cys	Lys	Thr	Cys 265	Ser	Ser	Cys	Arg	Asp 270	Gln	Gly
Lys	Asn	Ala 275	Asp	Asn	Met	Leu	Phe 280	Сув	Asp	Ser	Cys	Asp 285	Arg	Gly	Phe
His	Met 290	Glu	Cys	Cys	Asp	Pro 295	Pro	Leu	Thr	Arg	Met 300	Pro	Lys	Gly	Met
Trp 305	Ile	Cys	Gln	Ile	Cys 310	Arg	Pro	Arg	Lys	Lys 315	Gly	Arg	Lys	Leu	Leu 320
Gln	Lys	Lys	Ala	Ala 325	Gln	Ile	Lys	Arg	Arg 330	Tyr	Thr	Asn	Pro	Ile 335	Gly
Arg	Pro	Lys	Asn 340	Arg	Leu	Lys	Lys	Gln 345	Asn	Thr	Val	Ser	Lys 350	Gly	Pro
Phe	Ser	Lys 355	Val	Arg	Thr	Gly	Pro 360	Gly	Arg	Gly	Arg	Lys 365	Arg	Lys	Ile
Thr	Leu 370	Ser	Ser	Gln	Ser	Ala 375	Ser	Ser	Ser	Ser	Glu 380	Glu	Gly	Tyr	Leu
Glu 385	Arg	Ile	Asp	Gly	Leu 390	Asp	Phe	Cys	Arg	Asp 395	Ser	Asn	Val	Ser	Leu 400
Arg	Phe	Asn	Lys	Lys 405	Thr	Lys	Gly	Leu	Ile 410	Asp	Gly	Leu	Thr	Lуs 415	Phe
Phe	Thr	Pro	Ser 420	Pro	Asp	Gly	Arg	Lys 425	Ala	Arg	Gly	Glu	Val 430	Val	Asp
Tyr	Ser	Glu 435	Gln	Tyr	Arg	Ile	Arg 440	Lys	Arg	Gly	Asn	Arg 445	Lys	Ser	Ser
Thr	Ser 450	Asp	Trp	Pro	Thr	Asp 455	Asn	Gln	Asp	Gly	Trp 460	Asp	Gly	Lys	Gln

Glu 465	Asn	Glu	Glu	Arg	Leu 470	Phe	Gly	Ser	Gln	Glu 475	Ile	Met	Thr	Glu	Lys 480
Asp	Met	Glu	Leu	Phe 485	Arg	Asp	Ile	Gln	Glu 490	Gln	Ala	Leu	Gln	Lys 495	Val
Gly	Val	Thr	Gly 500	Pro	Pro	Asp	Pro	Gln 505	Val	Arg	Cys	Pro	Ser 510	Val	Ile
Glu	Phe	Gly 515	Lys	Tyr	Glu	Ile	His 520	Thr	Trp	Tyr	Ser	Ser 525	Pro	Tyr	Pro
Gln	Glu 530	Tyr	Ser	Arg	Leu	Pro 535	Lys	Leu	Tyr	Leu	Cys 540	Glu	Phe	Cys	Leu
Lys 545	Tyr	Met	Lys	Ser	Arg 550	Thr	Ile	Leu	Gln	Gln 555	His	Met	Lys	Lys	Cys 560
Gly	Trp	Phe	His	Pro 565	Pro	Ala	Asn	Glu	Ile 570	Tyr	Arg	Lys	Asn	Asn 575	Ile
Ser	Val	Phe	Glu 580	Val	Asp	Gly	Asn	Val 585	Ser	Thr	Ile	Tyr	Сув 590	Gln	Asn
Leu	Cys	Ьеи 595	Leu	Ala	Lys	Leu	Phe 600	Leu	Asp	His	Lys	Thr 605	Leu	Tyr	Tyr
Asp	Val 610	Glu	Pro	Phe	Leu	Phe 615	Tyr	Val	Leu	Thr	Gln 620	Asn	Asp	Val	Lys
Gly 625	Cys	His	Leu	Val	Gly 630	Tyr	Phe	Ser	Lys	Glu 635	Lys	His	Суз	Gln	Gln 640
Lys	Tyr	Asn	Val	Ser 645	Сув	Ile	Met	Ile	Ьеи 650	Pro	Gln	Tyr	Gln	Arg 655	Lys
Gly	Tyr	Gly	Arg 660	Phe	Leu	Ile	Asp	Phe 665	Ser	Tyr	Leu	Leu	Ser 670	Lys	Arg
Glu	Gly	Gln 675	Ala	Gly	Ser	Pro	Glu 680	Lys	Pro	Leu	Ser	Asp 685	Leu	Gly	Arg
Leu	Ser 690	Tyr	Met	Ala	Tyr	Trp 695	Lys	Ser	۷al	Ile	Leu 700	Glu	Cys	Leu	Tyr
His 705	Gln	Asn	Asp	Lys	Gln 710	Ile	Ser	Ile	Lys	Lys 715	Leu	Ser	ГÀв	Leu	Thr 720
Gly	Ile	Cys	Pro	Gln 725	Asp	Ile	Thr	Ser	Thr 730	Leu	His	His	Leu	Arg 735	Met
Leu	Asp	Phe	Arg 740	Ser	Asp	Gln	Phe	Val 745	Ile	Ile	Arg	Arg	Glu 750	Lys	Leu
Ile	Gln	Asp 755	His	Met	Ala	Lys	Leu 760	Gln	Leu	Asn	Leu	Arg 765	Pro	Val	Asp

### 192/299

Val Asp Pro Glu Cys Leu Arg Trp Thr Pro Val Ile Val Ser Asn Ser 775 Glu Pro Gln Cys Gln Glu Arg Glu Leu Glu Ile Ser Val Gly Lys Ser 805 810 Val Ser His Glu Asn Lys Glu Gln Asp Ser Tyr Ser Val Glu Ser Glu Lys Lys Pro Glu Val Met Ala Pro Val Ser Ser Thr Arg Leu Ser Lys 840 Gln Val Leu Pro His Asp Ser Leu Pro Ala Asn Ser Gln Pro Ser Arg Arg Gly Arg Trp Gly Arg Lys Asn Arg Lys Thr Gln Glu Arg Phe Gly Asp Lys Asp Ser Lys Leu Leu Glu Glu Thr Ser Ser Ala Pro Gln 885 Glu Gln Tyr Gly Glu Cys Gly Glu Lys Ser Glu Ala Thr Gln Glu Gln 905 Tyr Thr Glu Ser Glu Glu Gln Leu Val Ala Ser Glu Glu Gln Pro Ser 915 920 Gln Asp Gly Lys Pro Asp Leu Pro Lys Arg Arg Leu Ser Glu Gly Val 935 Glu Pro Trp Arg Gly Gln Leu Lys Lys Ser Pro Glu Ala Leu Lys Cys 950 945 955 Arg Leu Thr Glu Gly Ser Glu Arg Leu Pro Arg Arg Tyr Ser Glu Gly 965 970 Asp Arg Ala Val Leu Arg Gly Phe Ser Glu Ser Ser Glu Glu Glu Glu Glu Pro Glu Ser Pro Arg Ser Ser Pro Pro Ile Leu Thr Lys Pro Thr Leu Lys Arg Lys Lys Pro Phe Leu His Arg Arg Arg Arg Val Arg Lys Arg Lys His His Asn Ser Ser Val Val Thr Glu Thr Ile Ser Glu Thr Thr Glu Val Leu Asp Glu Pro Phe Glu Asp Ser Asp Ser Glu Arg 1050 Pro Met Pro Arg Leu Glu Pro Thr Phe Glu Ile Asp Glu Glu Glu Glu Glu Glu Asp Glu Asn Glu Leu Phe Pro Arg Glu Tyr Phe Arg Arg Leu

193/299

1085

Ser Ser Gln Asp Val Leu Arg Cys Gln Ser Ser Ser Lys Arg Lys Ser

1080

1075

Ser Ser Gin Asp Val Leu Arg Cys Gin Ser Ser Ser Lys Arg Lys Ser 1090 1095 1100

- Lys Asp Glu Glu Glu Asp Glu Glu Ser Asp Asp Ala Asp Asp Thr Pro 1105 1110 1115 1120
- Ile Leu Lys Pro Val Ser Leu Leu Arg Lys Arg Asp Val Lys Asn Ser 1125 1130 1135
- Pro Leu Glu Pro Asp Thr Ser Thr Pro Leu Lys Lys Lys Gly Trp 1140 1145 1150
- Pro Lys Gly Lys Ser Arg Lys Pro Ile His Trp Lys Lys Arg Pro Gly
  1155 1160 1165
- Arg Lys Pro Gly Phe Lys Leu Ser Arg Glu Ile Met Pro Val Ser Thr 1170 1180
- Gln Ala Cys Val Ile Glu Pro Ile Val Ser Ile Pro Lys Ala Gly Arg 1185 1190 1195 1200
- Lys Pro Lys Ile Gln Glu Ser Glu Glu Thr Val Glu Pro Lys Glu Asp 1205 1210 1215
- Met Pro Leu Pro Glu Glu Arg Lys Glu Glu Glu Met Gln Ala Glu 1220 1225 1230
- Ala Glu Glu Glu Glu Glu Glu Glu Asp Ala Ala Ser Ser Glu 1235 1240 1245
- Val Pro Ala Ala Ser Pro Ala Asp Ser Ser Asn Ser Pro Glu Thr Glu 1250 1255 1260
- Thr Lys Glu Pro Glu Val Glu Glu Glu Glu Glu Lys Pro Arg Val Ser 1265 1270 1275 1280
- Glu Glu Gln Arg Gln Ser Glu Glu Glu Gln Glu Leu Glu Glu Pro 1285 1290 1295
- Glu Pro Glu Glu Glu Glu Asp Ala Ala Glu Thr Ala Gln Asn Asp 1300 1305 1310
- Asp His Asp Ala Asp Asp Glu Asp Asp Gly His Leu Glu Ser Thr Lys
  1315 1320 1325
- Lys Lys Glu Leu Glu Glu Gln Pro Thr Arg Glu Asp Val Lys Glu Glu 1330 1340
- Pro Gly Val Gln Glu Ser Phe Leu Asp Ala Asn Met Gln Lys Ser Arg 1345 1350 1355 1360
- Glu Lys Ile Lys Asp Lys Glu Glu Thr Glu Leu Asp Ser Glu Glu Glu 1365 1370 1375
- Gln Pro Ser His Asp Thr Ser Val Val Ser Glu Gln Met Ala Gly Ser 1380 1385 1390

### 194/299

Glu Asp Asp His Glu Glu Asp Ser His Thr Lys Glu Glu Leu Ile Glu 1395 1400 1405

- Leu Lys Glu Glu Glu Glu Ile Pro His Ser Glu Leu Asp Leu Glu Thr 1410 1415 1420
- Val Gln Ala Val Gln Ser Leu Thr Gln Glu Glu Ser Ser Glu His Glu 1425 1430 1435 1440
- Gly Ala Tyr Gln Asp Cys Glu Glu Thr Leu Ala Ala Cys Gln Thr Leu 1445 1450 1455
- Gln Ser Tyr Thr Gln Ala Asp Glu Asp Pro Gln Met Ser Met Val Glu 1460 1465 1470
- Asp Cys His Ala Ser Glu His Asn Ser Pro Ile Ser Ser Val Gln Ser 1475 1480 1485
- His Pro Ser Gln Ser Val Arg Ser Val Ser Ser Pro Asn Val Pro Ala 1490 1495 1500
- Leu Glu Ser Gly Tyr Thr Gln Ile Ser Pro Glu Gln Gly Ser Leu Ser 1505 1510 1515 1520
- Ala Pro Ser Met Gln Asn Met Glu Thr Ser Pro Met Met Asp Val Pro
  1525 1530 1535
- Ser Val Ser Asp His Ser Gln Gln Val Val Asp Ser Gly Phe Ser Asp 1540 1545 1550
- Leu Gly Ser Ile Glu Ser Thr Thr Glu Asn Tyr Glu Asn Pro Ser Ser 1555 1560 1565
- Tyr Asp Ser Thr Met Gly Gly Ser Ile Cys Gly Asn Ser Ser Ser Gln
  1570 1580
- Ser Ser Cys Ser Tyr Gly Gly Leu Ser Ser Ser Ser Ser Leu Thr Gln 1585 1590 1595 1600
- Ser Ser Cys Val Val Thr Gln Gln Met Ala Ser Met Gly Ser Ser Cys 1605 1610 1615
- Ser Met Met Gln Gln Ser Ser Val Gln Pro Ala Ala Asn Cys Ser Ile 1620 1625 1630
- Lys Ser Pro Gln Ser Cys Val Val Glu Arg Pro Pro Ser Asn Gln Gln 1635 1640 1645
- Gln Gln Pro Pro Pro Pro Pro Pro Gln Gln Pro Gln Pro Pro Pro Pro 1650 1660
- Gln Pro Gln Pro Ala Pro Gln Pro Pro Pro Pro Gln Gln Gln Pro Gln 1665 1670 1675 1680

#### 195/299

Gln Gln Gln Pro Pro Leu Ser Gln Cys Ser Met Asn Asn Ser Phe Thr 1700 1705 1710

- Pro Ala Pro Met Ile Met Glu Ile Pro Glu Ser Gly Ser Thr Gly Asn 1715 1720 1725
- Ile Ser Ile Tyr Glu Arg Ile Pro Gly Asp Phe Gly Ala Gly Ser Tyr 1730 1735 1740
- Ser Gln Pro Ser Ala Thr Phe Ser Leu Ala Lys Leu Gln Gln Leu Thr 1745 1750 1755 1760
- Asn Thr Ile Met Asp Pro His Ala Met Pro Tyr Ser His Ser Pro Ala 1765 1770 1775
- Val Thr Ser Tyr Ala Thr Ser Val Ser Leu Ser Asn Thr Gly Leu Ala 1780 1785 1790
- Gln Leu Ala Pro Ser His Pro Leu Ala Gly Thr Pro Gln Ala Gln Ala 1795 1800 1805
- Thr Met Thr Pro Pro Pro Asn Leu Ala Ser Thr Thr Met Asn Leu Thr 1810 1815 1820
- Ser Pro Leu Gln Cys Asn Met Ser Ala Thr Asn Ile Gly Ile Pro 1825 1830 1835 1840
- His Thr Gln Arg Leu Gln Gly Gln Met Pro Val Lys Gly His Ile Ser 1845 1850 1855
- Ile Arg Ser Lys Ser Ala Pro Leu Pro Ser Ala Ala Ala His Gln Gln 1860 1865 1870
- Gln Leu Tyr Gly Arg Ser Pro Ser Ala Val Ala Met Gln Ala Gly Pro 1875 1880 1885
- Arg Ala Leu Ala Val Gln Arg Gly Met Asn Met Gly Val Asn Leu Met 1890 1895 1900
- Pro Thr Pro Ala Tyr Asn Val Asn Ser Met Asn Met Asn Thr Leu Asn 1905 1910 1915 1920
- Ala Met Asn Ser Tyr Arg Met Thr Gln Pro Met Met Asn Ser Ser Tyr 1925 1930 1935
- His Ser Asn Pro Ala Tyr Met Asn Gln Thr Ala Gln Tyr Pro Met Gln
  1940 1945 1950
- Met Gln Met Gly Met Met Gly Ser Gln Ala Tyr Thr Gln Gln Pro Met 1955 1960 1965
- Gln Pro Asn Pro His Gly Asn Met Met Tyr Thr Gly Pro Ser His His 1970 1975 1980
- Ser Tyr Met Asn Ala Ala Gly Val Pro Lys Gln Ser Leu Asn Gly Pro 1985 1990 1995 2000

Tyr Met Arg Arg

PCT/US02/06518

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PCT/US02/06518

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	acactgaaag					
	ctgaccttcc					
	aaagccctga					
	acagtgaggg					
	agccggaaag					
	agaaaccatt					
	tagtcacaga					
	actccgagag					
	aagaggatga					
	tactcaggtg					
	cagatgatgc					
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	ccaaaggcaa					
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	ccgaagagga					
	aggacgacca					
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	aagaagaaag					
	gtcagaccct					
	actgtcatgc					
	cagtccgttc					
	gcccagaaca					
	tggatgtgcc					
	tgggcagcat					
	tgggcggcag					
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198/299

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<211> 2442

<212> PRT

<213> Homo sapiens

<400> 252

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Leu Phe Asp Leu Glu Asn Asp Leu Pro Asp Glu Leu Ile Pro Asn Gly 35 40 45

Gly Glu Leu Gly Leu Leu Asn Ser Gly Asn Leu Val Pro Asp Ala Ala 50 55 60

Ser Lys His Lys Gln Leu Ser Glu Leu Leu Arg Gly Gly Ser Gly Ser 65 70 75 80

Ser Ile Asn Pro Gly Ile Gly Asn Val Ser Ala Ser Ser Pro Val Gln 85 90 95

Gln Gly Leu Gly Gly Gln Ala Gln Gly Gln Pro Asn Ser Ala Asn Met
100 105 110

Ala Ser Leu Ser Ala Met Gly Lys Ser Pro Leu Ser Gln Gly Asp Ser 115 120 125

Ser Ala Pro Ser Leu Pro Lys Gln Ala Ala Ser Thr Ser Gly Pro Thr 130 135 140

Pro 145	Ala	Ala	Ser	Gln	Ala 150	Leu	Asn	Pro	Gln	Ala 155	Gln	Lys	Gln	Val	Gly 160
Leu	Ala	Thr	Ser	Ser 165	Pro	Ala	Thr	Ser	Gln 170	Thr	Gly	Pro	Gly	Ile 175	Суѕ
Met	Asn	Ala	Asn 180	Phe	Asn	Gln	Thr	His 185	Pro	Gly	Leu	Leu	Asn 190	Ser	Asn
Ser	Gly	His 195	Ser	Leu	Ile	Asn	Gln 200	Ala	Ser	Gln	Gly	Gln 205	Ala	Gln	Val
Met	Asn 210	Gly	Ser	Leu	Gly	Ala 215	Ala	Gly	Arg	Gly	Arg 220	Gly	Ala	Gly	Met
Pro 225	Tyr	Pro	Thr	Pro	Ala 230	Met	Gln	Gly	Ala	Ser 235	Ser	Ser	Val	Leu	Ala 240
Glu	Thr	Leu	Thr	Gln 245	Val	Ser	Pro	Gln	Met 250	Thr	Gly	His	Ala	Gly 255	Leu
Asn	Thr	Ala	Gln 260	Ala	Gly	Gly	Met	Ala 265	Lys	Met	Gly	Ile	Thr 270	Gly	Asn
Thr	Ser	Pro 275	Phe	Gly	Gln	Pro	Phe 280	Ser	Gln	Ala	Gly	Gly 285	Gln	Pro	Met
Gly	Ala 290	Thr	Gly	Val	Asn	Pro 295	Gln	Leu	Ala	Ser	Lys 300	Gln	Ser	Met	Val
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Thr	Gln	Ala	Ile 340	Ala	Thr	Gly	Pro	Thr 345	Ala	Asp	Pro	Glu	Lys 350	Arg	Lys
Leu	Ile	Gln 355	Gln	Gln	Leu	Val	Leu 360	Leu	Leu	His	Ala	His 365	Lys	Cys	Gln
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Сув 385	Arg	Thr	Met	Lys	Asn 390	Val	Leu	Asn	His	Met 395	Thr	His	Cys	Gln	Ala 400
Gly	Lys	Ala	Cys	Gln 405	Val	Ala	His	Cys	Ala 410	Ser	Ser	Arg	Gln	Ile 415	Ile
Ser	His	Trp	Lys 420	Asn	Cys	Thr	Arg	His 425	Asp	Cys	Pro	Val	Cys 430	Leu	Pro
Leu	Lys	Asn 435	Ala	Ser	Asp	Lys	Arg 440	Asn	Gln	Gln	Thr	Ile 445	Leu	Gly	Ser

Pro	Ala 450	Ser	Gly	Ile	Gln	Asn 455	Thr	Ile	Gly	Ser	Val 460	Gly	Thr	Gly	Gln
Gln 465	Asn	Ala	Thr	Ser	Leu 470	Ser	Asn	Pro	Asn	Pro 475	Ile	Asp	Pro	Ser	Ser 480
Met	Gln	Arg	Ala	Tyr 485	Ala	Ala	Leu	Gly	Leu 490		Tyr	Met	Asn	Gln 495	Pro
Gln	Thr	Gln	Leu 500	Gln	Pro	Gln	Val	Pro 505	Gly	Gln	Gln	Pro	Ala 510	Gln	Pro
Gln	Thr	His 515	Gln	Gln	Met	Arg	Thr 520	Leu	Asn	Pro	Leu	Gly 525	Asn	Asn	Pro
Met	Asn 530	Ile	Pro	Ala	Gly	Gly 535	Ile	Thr	Thr	Asp	Gln 540	Gln	Pro	Pro	Asn
Leu 545	Ile	Ser	Glu	Ser	Ala 550	Leu	Pro	Thr	Ser	Leu 555	Gly	Ala	Thr	Asn	Pro 560
Leu	Met	Asn	Asp	Gly 565	Ser	Asn	Ser	Gly	Asn 570	Ile	Gly	Thr	Leu	Ser 575	Thr
Ile	Pro	Thr	Ala 580	Ala	Pro	Pro	Ser	Ser 585	Thr	Gly	Val	Arg	Lys 590	Gly	Trp
His	Glu	His 595	Val	Thr	Gln	Asp	Leu 600	Arg	Ser	His	Leu	Val 605	His	Lys	Leu
Val	Gln 610	Ala	Ile	Phe	Pro	Thr 615	Pro	Asp	Pro	Ala	Ala 620	Leu	Lys	Asp	Arg
Arg 625	Met	Glu	Asn	Leu	Val 630	Ala	Tyr	Ala	Lys	Lуs 635	Val	Glu	Gly	Asp	Met 640
Tyr	Glu	Ser	Ala	Asn 645	Ser	Arg	Asp	Glu	Tyr 650	Tyr	His	Leu	Leu	Ala 655	Glu
Lys	Ile	Tyr	Lys 660	Ile	Gln	Lys	Glu	Leu 665	Glu	Glu	Lys	Arg	Arg 670	Ser	Arg
Leu	His	Lys 675	Gln	Gly	Ile	Leu	Gly 680	Asn	Gln	Pro	Ala	Leu 685	Pro	Ala	Pro
Gly	Ala 690	Gln	Pro	Pro	Val	Ile 695	Pro	Gln	Ala	Gln	Pro 700	Val	Arg	Pro	Pro
Asn 705	Gly	Pro	Leu	Ser	Leu 710	Pro	Val	Asn	Arg	Met 715	Gln	Val	Ser	Gln	Gly 720
Met	Asn	Ser	Phe	Asn 725	Pro	Met	Ser	Leu	Gly 730	Asn	Val	Gln	Leu	Pro 735	Gln
Ala	Pro	Met	Gly 740	Pro	Arg	Ala	Ala	Ser 745	Pro	Met	Asn	His	Ser 750	Val	Gln
Met	Asn	Ser	Met	Gly	Ser	Val	Pro	Gly	Met	Ala	Ile	Ser	Pro	Ser	Arg

201/299

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#### 202/299

Gln Ser Thr Ser Pro Ser Gln Pro Arg Lys Lys Ile Phe Lys Pro Glu 1075 1080 1085

- Glu Leu Arg Gln Ala Leu Met Pro Thr Leu Glu Ala Leu Tyr Arg Gln 1090 1095 1100
- Asp Pro Glu Ser Leu Pro Phe Arg Gln Pro Val Asp Pro Gln Leu Leu 1105 1110 1115 1120
- Gly Ile Pro Asp Tyr Phe Asp Ile Val Lys Asn Pro Met Asp Leu Ser 1125 1130 1135
- Thr Ile Lys Arg Lys Leu Asp Thr Gly Gln Tyr Gln Glu Pro Trp Gln 1140 1145 1150
- Tyr Val Asp Asp Val Trp Leu Met Phe Asn Asn Ala Trp Leu Tyr Asn 1155 1160 1165
- Arg Lys Thr Ser Arg Val Tyr Lys Phe Cys Ser Lys Leu Ala Glu Val 1170 1175 1180
- Phe Glu Gln Glu Ile Asp Pro Val Met Gln Ser Leu Gly Tyr Cys Cys 1185 1190 1195 1200
- Gly Arg Lys Tyr Glu Phe Ser Pro Gln Thr Leu Cys Cys Tyr Gly Lys 1205 1210 1215
- Gln Leu Cys Thr Ile Pro Arg Asp Ala Ala Tyr Tyr Ser Tyr Gln Asn 1220 1225 1230
- Arg Tyr His Phe Cys Glu Lys Cys Phe Thr Glu Ile Gln Gly Glu Asn 1235 1240 1245
- Val Thr Leu Gly Asp Asp Pro Ser Gln Pro Gln Thr Thr Ile Ser Lys 1250 1255 1260
- Asp Gln Phe Glu Lys Lys Lys Asn Asp Thr Leu Asp Pro Glu Pro Phe 1265 1270 1275 1280
- Val Asp Cys Lys Glu Cys Gly Arg Lys Met His Gln Ile Cys Val Leu 1285 1290 1295
- His Tyr Asp Ile Ile Trp Pro Ser Gly Phe Val Cys Asp Asn Cys Leu 1300 1305 1310
- Lys Lys Thr Gly Arg Pro Arg Lys Glu Asn Lys Phe Ser Ala Lys Arg 1315 1320 1325
- Leu Gln Thr Thr Arg Leu Gly Asn His Leu Glu Asp Arg Val Asn Lys
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- Phe Leu Arg Arg Gln Asn His Pro Glu Ala Gly Glu Val Phe Val Arg 1345 1350 1355 1360
- Val Val Ala Ser Ser Asp Lys Thr Val Glu Val Lys Pro Gly Met Lys 1365 1370 1375

#### 203/299

Ser Arg Phe Val Asp Ser Gly Glu Met Ser Glu Ser Phe Pro Tyr Arg 1380 1385 1390

- Thr Lys Ala Leu Phe Ala Phe Glu Glu Ile Asp Gly Val Asp Val Cys 1395 1400 1405
- Phe Phe Gly Met His Val Gln Glu Tyr Gly Ser Asp Cys Pro Pro Pro 1410 1415 1420
- Asn Thr Arg Arg Val Tyr Ile Ser Tyr Leu Asp Ser Ile His Phe 1425 1430 1435 1440
- Arg Pro Arg Cys Leu Arg Thr Ala Val Tyr His Glu Ile Leu Ile Gly
  1445 1450 1455
- Tyr Leu Glu Tyr Val Lys Lys Leu Gly Tyr Val Thr Gly His Ile Trp
  1460 1465 1470
- Ala Cys Pro Pro Ser Glu Gly Asp Asp Tyr Ile Phe His Cys His Pro 1475 1480 1485
- Pro Asp Gln Lys Ile Pro Lys Pro Lys Arg Leu Gln Glu Trp Tyr Lys 1490 1495 1500
- Lys Met Leu Asp Lys Ala Phe Ala Glu Arg Ile Ile His Asp Tyr Lys 1505 1510 1515 1520
- Asp Ile Phe Lys Gln Ala Thr Glu Asp Arg Leu Thr Ser Ala Lys Glu 1525 1530 1535
- Leu Pro Tyr Phe Glu Gly Asp Phe Trp Pro Asn Val Leu Glu Glu Ser 1540 1545 1550
- Ile Lys Glu Leu Glu Glu Glu Glu Glu Glu Arg Lys Lys Glu Glu Ser 1555 1560 1565
- Thr Ala Ala Ser Glu Thr Thr Glu Gly Ser Gln Gly Asp Ser Lys Asn 1570 1580
- Ala Lys Lys Lys Asn Asn Lys Lys Thr Asn Lys Asn Lys Ser Ser Ile 1585 1590 1595 1600
- Ser Arg Ala Asn Lys Lys Lys Pro Ser Met Pro Asn Val Ser Asn Asp 1605 1610 1615
- Leu Ser Gln Lys Leu Tyr Ala Thr Met Glu Lys His Lys Glu Val Phe 1620 1625 1630
- Phe Val Ile His Leu His Ala Gly Pro Val Ile Asn Thr Leu Pro Pro 1635 1640 1645
- Ile Val Asp Pro Asp Pro Leu Leu Ser Cys Asp Leu Met Asp Gly Arg 1650 1655 1660
- Asp Ala Phe Leu Thr Leu Ala Arg Asp Lys His Trp Glu Phe Ser Ser 1665 1670 1675 1680
- Leu Arg Arg Ser Lys Trp Ser Thr Leu Cys Met Leu Val Glu Leu His

204/299

1685 1690 1695

Thr Gln Gly Gln Asp Arg Phe Val Tyr Thr Cys Asn Glu Cys Lys His 1700 1705 1710

- His Val Glu Thr Arg Trp His Cys Thr Val Cys Glu Asp Tyr Asp Leu 1715 1720 1725
- Cys Ile Asn Cys Tyr Asn Thr Lys Ser His Ala His Lys Met Val Lys 1730 1735 1740
- Trp Gly Leu Gly Leu Asp Asp Glu Gly Ser Ser Gln Gly Glu Pro Gln 1745 1750 1755 1760
- Ser Lys Ser Pro Gln Glu Ser Arg Arg Leu Ser Ile Gln Arg Cys Ile 1765 1770 1775
- Gln Ser Leu Val His Ala Cys Gln Cys Arg Asn Ala Asn Cys Ser Leu 1780 1785 1790
- Pro Ser Cys Gln Lys Met Lys Arg Val Val Gln His Thr Lys Gly Cys 1795 1800 1805
- Lys Arg Lys Thr Asn Gly Gly Cys Pro Val Cys Lys Gln Leu Ile Ala 1810 1815 1820
- Leu Cys Cys Tyr His Ala Lys His Cys Gln Glu Asn Lys Cys Pro Val 1825 1830 1835 1840
- Pro Phe Cys Leu Asn Ile Lys His Lys Leu Arg Gln Gln Gln Ile Gln 1845 1850 1855
- His Arg Leu Gln Gln Ala Gln Leu Met Arg Arg Met Ala Thr Met 1860 1865 1870
- Asn Thr Arg Asn Val Pro Gln Gln Ser Leu Pro Ser Pro Thr Ser Ala 1875 1880 1885
- Pro Pro Gly Thr Pro Thr Gln Gln Pro Ser Thr Pro Gln Thr Pro Gln 1890 1895 1900
- Pro Pro Ala Gln Pro Gln Pro Ser Pro Val Ser Met Ser Pro Ala Gly 1905 1910 1915 1920
- Phe Pro Ser Val Ala Arg Thr Gln Pro Pro Thr Thr Val Ser Thr Gly 1925 1930 1935
- Lys Pro Thr Ser Gln Val Pro Ala Pro Pro Pro Pro Ala Gln Pro Pro 1940 1945 1950
- Pro Ala Ala Val Glu Ala Ala Arg Gln Ile Glu Arg Glu Ala Gln Gln 1955 1960 1965
- Gln Gln His Leu Tyr Arg Val Asn Ile Asn Asn Ser Met Pro Pro Gly 1970 1975 1980
- Arg Thr Gly Met Gly Thr Pro Gly Ser Gln Met Ala Pro Val Ser Leu 1985 1990 1995 2000

#### 205/299

Asn Val Pro Arg Pro Asn Gln Val Ser Gly Pro Val Met Pro Ser Met 2005 2010 2015

- Pro Pro Gly Gln Trp Gln Gln Ala Pro Leu Pro Gln Gln Gln Pro Met
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- Pro Gly Leu Pro Arg Pro Val Ile Ser Met Gln Ala Gln Ala Val 2035 2040 2045
- Ala Gly Pro Arg Met Pro Ser Val Gln Pro Pro Arg Ser Ile Ser Pro 2050 2055 2060
- Ser Ala Leu Gln Asp Leu Leu Arg Thr Leu Lys Ser Pro Ser Ser Pro 2065 2070 2075 2080
- Gln Gln Gln Gln Val Leu Asn Ile Leu Lys Ser Asn Pro Gln Leu 2085 2090 2095
- Met Ala Ala Phe Ile Lys Gln Arg Thr Ala Lys Tyr Val Ala As<br/>n Gln 2100 2105 2110
- Pro Gly Met Gln Pro Gln Pro Gly Leu Gln Ser Gln Pro Gly Met Gln 2115 2120 2125
- Pro Gln Pro Gly Met His Gln Gln Pro Ser Leu Gln Asn Leu Asn Ala 2130 2135 2140
- Met Gln Ala Gly Val Pro Arg Pro Gly Val Pro Pro Gln Gln Gln Ala 2145 2150 2155 2160
- Met Gly Gly Leu Asn Pro Gln Gly Gln Ala Leu Asn Ile Met Asn Pro 2165 2170 2175
- Gly His Asn Pro Asn Met Ala Ser Met Asn Pro Gln Tyr Arg Glu Met 2180 2185 2190
- Gln Gln Gln Gln Gln Gln Gln Gly Ser Ala Gly Met Ala Gly Gly 2210 2215 2220
- Met Ala Gly His Gly Gln Phe Gln Gln Pro Gln Gly Pro Gly Gly Tyr 2225 2230 2235 2240
- Pro Pro Ala Met Gln Gln Gln Gln Arg Met Gln Gln His Leu Pro Leu 2245 2250 2255
- Gln Gly Ser Ser Met Gly Gln Met Ala Ala Gln Met Gly Gln Leu Gly 2260 2265 2270
- Gln Met Gly Gln Pro Gly Leu Gly Ala Asp Ser Thr Pro Asn Ile Gln 2275 2280 2285
- Gln Ala Leu Gln Gln Arg Ile Leu Gln Gln Gln Gln Met Lys Gln Gln 2290 2295 2300

206/299

Ile Gly Ser Pro Gly Gln Pro Asn Pro Met Ser Pro Gln Gln His Met 2305 2310 2315 2320

Leu Ser Gly Gln Pro Gln Ala Ser His Leu Pro Gly Gln Gln Ile Ala 2325 2330 2335

Thr Ser Leu Ser Asn Gln Val Arg Ser Pro Ala Pro Val Gln Ser Pro 2340 2345 2350

Arg Pro Gln Ser Gln Pro Pro His Ser Ser Pro Ser Pro Arg Ile Gln
2355 2360 2365

Pro Gln Pro Ser Pro His His Val Ser Pro Gln Thr Gly Ser Pro His 2370 2380

Pro Gly Leu Ala Val Thr Met Ala Ser Ser Ile Asp Gln Gly His Leu 2385 2390 2395 2400

Gly Asn Pro Glu Gln Ser Ala Met Leu Pro Gln Leu Asn Thr Pro Ser 2405 2410 2415

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Asp Thr Leu Glu Lys Phe Val Glu Gly Leu 2435 2440

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<212> DNA

<213> Homo sapiens

<400> 253

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		ccctccagg				
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		agcccccagc		_		
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		cagtcccagc				
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		atagatcagg				
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209/299

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Leu His Val Pro Val Pro Arg Ala Leu Arg Met Glu Glu Asp Ser Ile 35 40 45

Arg Leu Pro Ala His Leu Arg Leu Gln Pro Ile Tyr Trp Ser Arg Asp 50 55 60

Asp Val Ala Gln Trp Leu Lys Trp Ala Glu Asn Glu Phe Ser Leu Arg 65 70 75 80

Pro Ile Asp Ser Asn Thr Phe Glu Met Asn Gly Lys Ala Leu Leu Leu 85 90 95

Leu Thr Lys Glu Asp Phe Arg Tyr Arg Ser Pro His Ser Gly Asp Val

Leu Tyr Glu Leu Leu Gln His Ile Leu Lys Gln Arg Lys Pro Arg Ile 115 120 125

Leu Phe Ser Pro Phe Phe His Pro Gly Asn Ser Ile His Thr Gln Pro 130 135 140

Glu Val Ile Leu His Gln Asn His Glu Glu Glu Ala Leu Gln Arg Pro 145 150 155 160

Val Ala Ser Asp Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala Arg Trp
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<213> Homo sapiens

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212/299

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Leu Glu Lys Lys Leu Ala Lys Ala Gln Cys Glu Gln Ser His Leu Met 50 55 60

Arg Glu His Glu Asp Val Gln Glu Arg Thr Thr Leu Arg Tyr Glu Glu 65 70 75 80

Arg Ile Thr Glu Leu His Ser Val Ile Ala Glu Leu Asn Lys Lys Ile 85 90 95

Asp Arg Leu Gln Gly Thr Thr Ile Arg Glu Glu Asp Glu Tyr Ser Glu
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Leu Arg Ser Glu Leu Ser Gln Ser Gln His Glu Val Asn Glu Asp Ser 115 120 125

Arg Ser Met Asp Gln Asp Gln Thr Ser Val Ser Ile Pro Glu Asn Gln 130 140

Ser Thr Met Val Thr Ala Asp Met Asp Asn Cys Ser Asp Leu Asn Ser 145 150 155 160

Glu Leu Gln Arg Val Leu Thr Gly Leu Glu Asn Val Val Cys Gly Arg 165 170 175

Lys Lys Ser Ser Cys Ser Leu Ser Val Ala Glu Val Asp Arg His Ile 180 \$180\$

Glu Gln Leu Thr Thr Ala Ser Glu His Cys Asp Leu Ala Ile Lys Thr 195  $\phantom{\bigg|}200\phantom{\bigg|}205\phantom{\bigg|}$ 

Val Glu Glu Glu Gly Val Leu Gly Arg Asp Leu Tyr Pro Asn Leu 210 215 220

Ala Glu Glu Arg Ser Arg Trp Glu Lys Glu Leu Ala Gly Leu Arg Glu 225 230 235 240

Glu Asn Glu Ser Leu Thr Ala Met Leu Cys Ser Lys Glu Glu Glu Leu 245 250 255

Asn Arg Thr Lys Ala Thr Met Asn Ala Ile Arg Glu Glu Arg Asp Arg 260 265 270

#### 213/299

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214/299

580 585 590 Ile His Ile Asp Pro Leu Ser Tyr Asp Val Lys Pro Arg Gly Asp Ser 600 Gln Arg Leu Asp Leu Glu Asn Ala Val Leu Met Gln Glu Leu Met Ala 615 Met Lys Glu Glu Met Ala Glu Leu Lys Ala Gln Leu Tyr Leu Leu Glu 630 635 Lys Glu Lys Lys Ala Leu Glu Leu Lys Leu Ser Thr Arg Glu Ala Gln Glu Gln Ala Tyr Leu Val His Ile Glu His Leu Lys Ser Glu Val Glu Glu Gln Lys Glu Gln Arg Met Arg Ser Leu Ser Ser Thr Ser Ser Gly 680 Ser Lys Asp Lys Pro Gly Lys Glu Cys Ala Asp Ala Ala Ser Pro Ala 695 Leu Ser Leu Ala Glu Leu Arg Thr Thr Cys Ser Glu Asn Glu Leu Ala 710 . 715 Ala Glu Phe Thr Asn Ala Ile Arg Arg Glu Lys Lys Leu Lys Ala Arg 725 730 Val Gln Glu Leu Val Ser Ala Leu Glu Arg Leu Thr Lys Ser Ser Glu 745 Ile Arg His Gln Gln Ser Ala Glu Phe Val Asn Asp Leu Lys Arg Ala 760 Asn Ser Asn Leu Val Ala Ala Tyr Glu Lys Ala Lys Lys Lys His Gln Asn Lys Leu Lys Lys Leu Glu Ser Gln Met Met Ala Met Val Glu Arg His Glu Thr Gln Val Arg Met Leu Lys Gln Arg Ile Ala Leu Leu Glu Glu Glu Asn Ser Arg Pro His Thr Asn Glu Thr Ser Leu 820

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Glu Cys Tyr Asn Leu Ser Pro Thr Lys Asp Lys Met Leu Val Ala Val
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Lys Ala Leu Lys Asp Pro Thr Leu Ala Ala Arg Lys Asp Phe Gln Arg
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217/299

Glu Ala Glu Leu Leu Thr Asn Leu Gln His Glu His Ile Val Lys Phe \$85\$ 90 95

Tyr Gly Val Cys Gly Asp Gly Asp Pro Leu Ile Met Val Phe Glu Tyr 100 105 110

Met Lys His Gly Asp Leu Asn Lys Phe Leu Arg Ala His Gly Pro Asp 115 120 125

Ala Met Ile Leu Val Asp Gly Gln Pro Arg Gln Ala Lys Gly Glu Leu 130 135 140

Gly Leu Ser Gln Met Leu His Ile Ala Ser Gln Ile Ala Ser Gly Met 145 150 155 160

Val Tyr Leu Ala Ser Gln His Phe Val His Arg Asp Leu Ala Thr Arg 165 170 175

Asn Cys Leu Val Gly Ala Asn Leu Leu Val Lys Ile Gly Asp Phe Gly 180 185 190

Met Ser Arg Asp Val Tyr Ser Thr Asp Tyr Tyr Arg Val Gly Gly His 195 200 205

Thr Met Leu Pro Ile Arg Trp Met Pro Pro Glu Ser Ile Met Tyr Arg 210 215 220

Lys Phe Thr Thr Glu Ser Asp Val Trp Ser Phe Gly Val Ile Leu Trp 225 230 235 240

Glu Ile Phe Thr Tyr Gly Lys Gln Pro Trp Phe Gln Leu Ser Asn Thr 245 250 255

Glu Val Ile Glu Cys Ile Thr Gln Gly Arg Val Leu Glu Arg Pro Arg 260 265 270

Val Cys Pro Lys Glu Val Tyr Asp Val Met Leu Gly Cys Trp Gln Arg 275 280 285

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Asn	Asn	His	Cys 20	Pro	Ala	Ser	Ser	Glu 25	Ser	His	Pro	Lys	Pro 30	Ser	Ser	
Pro	Arg	Gln 35	Glu	Ser	Thr	Arg	Val 40	Ile	Gln	Leu	Met	Pro 45	Ser	Pro	Ile	
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Ser 65	Arg	Leu	Ser	Glu	Asp 70	Gly	Leu	His	Arg	Glu 75	Gly	Lys	Pro	Ile	Asn 80	
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219/299

Asn Lys Phe Leu Arg Ala His Gly Pro Asp Ala Met Ile Leu Val Asp Gly Gln Pro Arg Gln Ala Lys Gly Glu Leu Gly Leu Ser Gln Met Leu 235 His Ile Ala Ser Gln Ile Ala Ser Gly Met Val Tyr Leu Ala Ser Gln His Phe Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu Val Gly Ala 265 Asn Leu Leu Val Lys Ile Gly Asp Phe Gly Met Ser Arg Asp Val Tyr 280 Ser Thr Asp Tyr Tyr Arg Val Gly Gly His Thr Met Leu Pro Ile Arg 295 Trp Met Pro Pro Glu Ser Ile Met Tyr Arg Lys Phe Thr Thr Glu Ser 305 Asp Val Trp Ser Phe Gly Val Ile Leu Trp Glu Ile Phe Thr Tyr Gly Lys Gln Pro Trp Phe Gln Leu Ser Asn Thr Glu Val Ile Glu Cys Ile Thr Gln Gly Arg Val Leu Glu Arg Pro Arg Val Cys Pro Lys Glu Val 360 Tyr Asp Val Met Leu Gly Cys Trp Gln Arg Glu Pro Gln Gln Arg Leu 375 Asn Ile Lys Glu Ile Tyr Lys Ile Leu His Ala Leu Gly Lys Ala Thr 395 Pro Ile Tyr Leu Asp Ile Leu Gly 405 <210> 272 <211> 1403 <212> DNA <213> Homo sapiens <400> 272

# 220/299

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Val Arg Glu Ser Glu Thr Thr Lys Gly Ala Tyr Cys Leu Ser Val Ser 180 185 190

Asp Phe Asp Asn Ala Lys Gly Leu Asn Val Lys His Tyr Lys Ile Arg

221/299

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223/299

Gln Asp Glu Phe Tyr Arg Ser Gly Trp Ala Leu Asn Met Lys Glu Leu 50 55 Lys Leu Leu Gln Thr Ile Gly Lys Gly Glu Phe Gly Asp Val Met Leu Gly Asp Tyr Arg Gly Asn Lys Val Ala Val Lys Cys Ile Lys Asn Asp 90 Ala Thr Ala Gln Ala Phe Leu Ala Glu Ala Ser Val Met Thr Gln Leu Arg His Ser Asn Leu Val Gln Leu Leu Gly Val Ile Val Glu Glu Lys 120 Gly Gly Leu Tyr Ile Val Thr Glu Tyr Met Ala Lys Gly Ser Leu Val 135 Asp Tyr Leu Arg Ser Arg Gly Arg Ser Val Leu Gly Gly Asp Cys Leu 150 Leu Lys Phe Ser Leu Asp Val Cys Glu Ala Met Glu Tyr Leu Glu Gly Asn Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Ser 185 Glu Asp Asn Val Ala Lys Val Ser Asp Phe Gly Leu Thr Lys Glu Ala Ser Thr Pro Arg Thr Arg Ala Ser Cys Gln Ser Ser Gly Gln Pro Leu Arg Pro 225 <210> 276 <211> 2442 <212> DNA <213> Homo sapiens <400> 276 tccggggcgg cccccggcag ccagcgcgac gttccaaaat cgaacctcag tggcggcgct 60 cggaagcgga actctgccgg ggccgcgccg gctacattgt gctgcggtcg actctagagg 120 ctccccttcc tcccccgac tccctccctc ccccttcccc cgcctttctt ccctccgcga 180 cccgggccgt gcgtccgtcc ccctgcctct gcctggcggt ccctcctccc ctctccttgc 240 acceatacet etttgtaceg caccecetgg gtatecetge geceeteece teccecetga 300 ccgcatggac cgtcccgcag gccgctgatg ccgcccgccq qacggtggcc cqqaccgcag 360 tgccccaaga gagctctaat ggtaccaagt gacaggttqq cttaactqaq actcqqggac 420 ccaagagctc ctgagaagat gtcagcaata caggccgcct gqccatccgg tacagaatgt 480 attgccaagt acaacttcca cggcactgcc gagcaggacc tgcccttctg caaaqgagac 540 gtgctcacca ttgtggccgt caccaaggac cccaactggt acaaagccaa aaacaaggtg 600 ggccgtgagg gcatcatccc agccaactac gtccagaagc gggagggcgt gaaggcgggt 660 accaaactca gcctcatgcc gtgagttcca cggcaagatc acacgggagc aggctgagcg 720 gettetgtac cegeeggaga caggeetgtt cetggtgegg gagageacca actaeccegg 780 agactacacg ctgtgcgtga gctgcgacgg caaggtggag cactaccgca tcatgtacca 840 tgccagcaag ctcagcatcg acgaggaggt gtactttgag aacctcatgc agctqgtgga 900

224/299

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Leu Asn Arg Ser Leu Asp His Ser Ser Trp Glu Lys Leu Ser Val Arg

Asn Arg Gly Phe Pro Leu Leu Thr Val Tyr Leu Lys Val Phe Leu Ser 115 120 125

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#### 227/299

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228/299

Ile Glu Asn Lys Leu Tyr Gly Met Ser Asp Pro Asn Trp Pro Gly Glu 1060 1065 1070

Ser Pro Val Pro Leu Thr Arg Ala Asp Gly Thr Asn Thr Gly Phe Pro 1075 1080 1085

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Asp Ile Glu Gln Trp Phe Thr Glu Asp Pro Gly Pro Asp Glu Ala Pro 50 55 60

Arg Met Pro Glu Ala Ala Pro Pro Val Ala Pro Ala Pro Ala Thr Pro

Thr Pro Ala Ala Pro Ala Pro Ala Pro Ser Trp Pro Leu Ser Ser Ser 85 90 95

Val Pro Ser Gln Lys Thr Tyr Gln Gly Ser Tyr Gly Phe Arg Leu Gly
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Phe Leu His Ser Gly Thr Ala Lys Ser Val Thr Cys Thr Tyr Ser Pro 115 120 125

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Leu Trp Val Asp Ser Thr Pro Pro Pro Gly Thr Arg Val Arg Ala Met 145 150 150 155 160

Ala Ile Tyr Lys Gln Ser Gln His Met Thr Glu Val Val Arg Arg Cys 165 170 175

Pro His His Glu Arg Cys Ser Asp Ser Asp Gly Leu Ala Pro Pro Gln
180 185 190

His Leu Ile Arg Val Glu Gly Asn Leu Arg Val Glu Tyr Leu Asp Asp 195 200 205

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229/299

Arg Asn Thr Phe Arg His Ser Val Val Val Pro Tyr Glu Pro Pro Glu Val Gly Ser Asp Cys Thr Thr Ile His Tyr Asn Tyr Met Cys Asn Ser 230 235 Ser Cys Met Gly Gly Met Asn Arg Arg Pro Ile Leu Thr Ile Ile Thr 250 Leu Glu Asp Ser Ser Gly Asn Leu Leu Gly Arg Asn Ser Phe Glu Val Arg Val Cys Ala Cys Pro Gly Arg Asp Arg Thr Glu Glu Glu Asn 280 Leu Arg Lys Lys Gly Glu Pro His His Glu Leu Pro Pro Gly Ser Thr Lys Arg Ala Leu Pro Asn Asn Thr Ser Ser Pro Gln Pro Lys Lys 315 310 Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg Glu 330 Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys Asp 345 Ala Gln Ala Gly Lys Glu Pro Gly Gly Ser Arg Ala His Ser Ser His Leu Lys Ser Lys Lys Gly Gln Ser Thr Ser Arg His Lys Lys Leu Met Phe Lys Thr Glu Gly Pro Asp Ser Asp 390 <210> 279 <211> 1303 <212> DNA <213> Homo sapiens <400> 279 gtccaggagc aggtagctgc tgggctccgg ggacactttg cgttcgggct gggagcgtgc 60 tttccacgac ggtgacacgc ttccctggat tggcagccag actgccttcc gggtcactgc 120 catggaggag ccgcagtcag atcctagcgt cgagcccct ctgagtcagg aaacattttc 180 agacctatgg aaactacttc ctgaaaacaa cgttctgtcc cccttgccgt cccaagcaat 240 ggatgatttg atgctgtccc cggacgatat tgaacaatgg ttcactgaag acccaggtcc 300 agatgaaget eecagaatge cagaggetge tececeegtg geecetgeac cagegactee 360 tacaccggcg gcccctgcac cagccccctc ctggcccctg tcatcttctg tcccttccca 420 gaaaacctac cagggcagct acggtttccg tctgggcttc ttgcattctg ggacagccaa 480 gtctgtgact tgcacgtact cccctgccct caacaagatg ttttgccaac tggccaagac 540 ctgccctgtg cagctgtggg ttgattccac accccgccc ggcacccgcg tccgcgccat 600 ggccatctac aagcagtcac agcacatgac ggaggttgtg aggcgctgcc cccaccatga 660 gcgctgctca gatagcgatg gtctggcccc tcctcagcat cttatccgag tggaaggaaa 720 tttgcgtgtg gagtatttgg atgacagaaa cacttttcga catagtgtgg tggtgcccta 780 tgagccgcct gaggttggct ctgactgtac caccatccac tacaactaca tgtgtaacag 840 ttcctgcatg ggcggcatga accggaggcc catcctcacc atcatcacac tggaagactc 900

PCT/US02/06518 **WO** 02/069900

# 230/299

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Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn 35 40 45	
Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu 50 55 60	
Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser 65 70 75 80	
Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn 85 90 95	
Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln 100 105 110	
Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser 115 120 125	
Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln 130 135 140	
Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys 145 150 155 160	
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Met Thr Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr 180 185 190	
Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His 195 200 205	
Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His 210 215 220	
Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro	

	231/299																
•	225					230					235					240	
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	Gly	Thr	Glu	Phe 260	Thr	Thr	Val	Leu	Tyr 265	Asn	Phe	Met	Cys	Asn 270	Ser	Ser	
	Cya	Val	Gly 275	Gly	Met	Asn	Arg	Arg 280	Pro	Ile	Leu	Ile	Ile 285	Val	Thr	Leu	
	Glu !	Thr 290	Arg	Asp	Gly	Gln	Val 295		Gly	Arg	Arg	Cys 300	Phe	Glu	Ala	Arg	
	Ile 305	Cys	Ala	Cys ,	Pro	Gly 310	Arg	Asp	Arg	Lys	Ala 315	Asp	Glu	Asp	Ser	Ile 320	
	Arg	Lys	Gln	Gln	Val 325	Ser	Asp	Ser	Thr	Lys 330	Asn	Gly	Asp	Gly	Thr 335	Lys	
	Arg	Pro	Phe	Arg 340	Gln	Asn	Thr	His	Gly 345	Ile	Gln	Met	Thr	Ser 350	Ile	Lys	
	Lys	Arg	Arg 355	Ser	Pro	Asp	Asp	Glu 360	Leu	Leu	Tyr	Leu	Pro 365	Val	Arg	Gly	
	Arg	Glu 370	Thr	Tyr	Glu	Met	Leu 375	Leu	Lys	Ile	Lys	Glu 380	Ser	Leu	Glu	Leu	
	Met 385	Gln	Tyr	Leu	Pro	Gln 390	His	Thr	Ile	Glu	Thr 395	Tyr	Arg	Gln	Gln	Gln 400	
	Gln	Gln	Gln	His	Gln 405	His	Leu	Leu	Gln	Lys 410	His	Leu	Leu	Ser	Ala 415	Cys	
	Phe	Arg	Asn	Glu 420	Leu	Val	Glu	Pro	Arg 425	Arg	Glu	Thr	Pro	Lуs 430	Gln	Ser	
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232/299

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				tccgcgccat						
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				atttcatgtg						
				ttactctgga						
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				cggacagtac						
				tccagatgac						
				tgaggggccg						
				agtaccttcc						
				acttacttca						
				gagaaactcc						
				tgtacccata						
				tgtgagtgtg						
				aagacacttt						
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	catgaaaccc tggaagacct actacaaaaa aactgttgtt tggcccccat agcaggtgaa									
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				ttccatttta						
				tccatcttcc						
				tgttattgag						
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<213> Homo	sapiens									
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1	5		10		15					
Gin His Ile		ne Leu Glu		Cys Ser Val						
	20		25	3 (	)					
T7 - 7 T	- Non Dha II		D G 61	n 01 1						
			rro ser Glu	Asp Gly Ala	a Thr Asn					
35	,	40		45						
Lvs Tle Cli	ı Tle Ser Ma	et Dan Gva	Tle Ara Met	Gln Asp Sei	. Ago Taga					
50	TIC DET M	sc Asp Cys . 55	TTE WIG	60 Sei	. wah men					
30		رر		50						

Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser

65					70					75					80
Met	qaA	Gln	Gln	Ile 85	Gln	Asn	Gly	Ser	Ser 90	Ser	Thr	Ser	Pro	Tyr 95	Asn
Thr	Asp	His	Ala 100	Gln	Asn	Ser	Val	Thr 105	Ala	Pro	Ser	Pro	Tyr 110	Ala	Gln
Pro	Ser	Ser 115	Thr	Phe	Asp	Ala	Leu 120	Ser	Pro	Ser	Pro	Ala 125	Ile	Pro	Ser
Asn	Thr 130	Asp	Tyr	Pro	Gly	Pro 135		Ser	Phe	Asp	Val 140	Ser	Phe	Gln	Gln
Ser 145	Ser	Thr	Ala	Lys	Ser 150	Ala	Thr	Trp	Thr	Tyr 155	Ser	Thr	Glu	Leu	Lуs 160
Lys	Leu	Tyr	Cys	Gln 165	Ile	Ala	Lys	Thr	Cys 170	Pro	Ile	Gln	Ile	Lys 175	Val
Met	Thr	Pro	Pro 180	Pro	Gln	Gly	Ala	Val 185	Ile	Arg	Ala	Met	Pro 190	Val	Tyr
Lys	Lys	Ala 195	Glu	His	Val	Thr	Glu 200	Val	Val	Lys	Arg	Cys 205	Pro	Asn	His
Glu	Leu 210	Ser	Arg	Glu	Phe	Asn 215	Glu	Gly	Gln	Ile	Ala 220	Pro	Pro	Ser	His
Leu 225	Ile	Arg	Val	Glu	Gly 230	Asn	Ser	His	Ala	Gln 235	Tyr	Val	Glu	Asp	Pro 240
Ile	Thr	Gly	Arg	Gln 245	Ser	Val	Leu	Val	Pro 250	Tyr	Glu	Pro	Pro	Gln 255	Val
Gly	Thr	Glu	Phe 260	Thr	Thr	Val	Leu	Tyr 265	Asn	Phe	Met	Cys	Asn 270		Ser
Cys	Val	Gly 275	Gly	Met	Asn	Arg	Arg 280	Pro	Ile	Leu	Ile	Ile 285	Val	Thr	Leu
Glu	Thr 290	Arg	Asp	Gly	Gln	Val 295	Leu	Gly	Arg	Arg	300	Phe	Glu	Ala	Arg
Ile 305	Cys	Ala	Cys	Pro	Gly 310	Arg	Asp	Arg	Lys	Ala 315	Asp	Glu	Asp	Ser	Ile 320
Arg	ГÀа	Gln	Gln	Val 325	Ser	Asp	Ser	Thr	Lys 330	Asn	Gly	Asp	Gly	Thr 335	Lys
Arg	Pro	Phe	Arg 340	Gln	Asn	Thr	His	Gly 345	Ile	Gln	Met	Thr	Ser 350	Ile	Lys
Lys	Arg	Arg 355	Ser	Pro	Asp	Asp	Glu 360	Leu	Leu	Tyr	Leu	Pro 365	Val	Arg	Gly
Arg	Glu 370	Thr	Tyr	Glu	Met	Leu 375	Leu	Lys	Ile	Lys	Glu 380	Ser	Leu	Glu	Leu

#### 234/299

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Glu

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<213> Homo sapiens

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235/299

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attgacttga actttgt	gga tgaaccatca	gaagatggtg	cgacaaacaa	gattgagatt	300
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catgcccagt atgtaga					
ccaccccagg ttggcac					
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gggcaagtcc tgggccg					
aggaaggcgg atgaaga					
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ttcccacccc gagatga					
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Met Ser Gln Ser Th			ser Pro GI		
1	5	10		15	
Gin His Tie Trn Ar	n Dhe Leu Clu	Gln Dro Tle	Cva Ser Ve	] Gln Dro	
Gln His Ile Trp As	h tire nea gia	25	Cys ser va.		
۵.0		دے	3	•	

Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn

Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu

50 55 60

## 236/299

Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn 90 Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln 105 Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr 180 185 Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His 200 Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro 230 Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val 245 250 Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys 345 Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu

237/299

370 375 380 Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln 390 395 Gln Gln His Gln His Leu Leu Gln Lys Gln Thr Ser Ile Gln Ser 405 Pro Ser Ser Tyr Gly Asn Ser Ser Pro Pro Leu Asn Lys Met Asn Ser 425 Met Asn Lys Leu Pro Ser Val Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Arg 455 Ser Gly Lys Ser Glu Asn Pro <210> 285 <211> 2031 <212> DNA <213> Homo sapiens <400> 285 tcgttgatat caaagacagt tgaaggaaat gaattttgaa acttcacggt gtgccaccct 60 acagtactgc cctgaccctt acatccaqcq tttcqtaqaa acccaqctca tttctcttqq 120 aaagaaagtt attaccgatc caccatqtcc caqaqcacac aqacaaatqa attcctcaqt 180 ccagaggttt tccagcatat ctgggatttt ctggaacagc ctatatgttc agttcagccc 240 attgacttga actttgtgga tgaaccatca gaagatggtg cgacaaacaa gattgagatt 300 agcatggact gtatccgcat gcaggactcg gacctgagtg accccatgtg gccacagtac 360 acgaacctgg ggctcctgaa cagcatqqac caqcaqattc aqaacqqctc ctcqtccacc 420 agtecetata acacagacea egegeagaae agegteaegg egecetegee etaegeaeag 480 cccageteca cettegatge teteteteca teaccegeca teccetecaa caccgactae 540 ccaggcccgc acagtttcga cgtgtccttc cagcagtcga gcaccgccaa gtcqqccacc 600 tggacgtatt ccactgaact gaagaaactc tactgccaaa ttgcaaagac atgccccatc 660 cagatcaagg tgatgacccc acctcctcag ggagctgtta tccgcgccat gcctgtctac 720 aaaaaagctg agcacgtcac ggaggtggtg aagcggtgcc ccaaccatga gctgagccgt 780 gaattcaacg agggacagat tgcccctcct agtcatttga ttcgagtaga ggggaacagc 840 catgcccagt atgtagaaga tcccatcaca ggaagacaga gtgtgctggt accttatgag 900 ccaccccagg ttggcactga attcacgaca gtcttgtaca atttcatgtg taacagcagt 960 tgtgttggag ggatgaaccg ccgtccaatt ttaatcattg ttactctgga aaccagagat 1020 gggcaagtcc tgggccgacg ctgctttgag gcccggatct gtgcttgccc aggaagagac 1080 aggaaggcgg atgaagatag catcagaaag cagcaagttt cggacagtac aaagaacggt 1140 gatggtacga agcgcccgtt tcgtcagaac acacatqqta tccagatqac atccatcaaq 1200 aaacgaagat ccccagatga tgaactgtta tacttaccaq tgaqggqccq tqaqacttat 1260 gaaatgctgt tgaagatcaa agagtccttg gaactcatgc agtaccttcc tcagcacaca 1320 attgaaacgt acaggcaaca gcaacagcag cagcaccagc acttacttca gaaacagacc 1380 tcaatacagt ctccatcttc atatggtaac agctccccac ctctgaacaa aatgaacagc 1440 atgaacaagc tgccttctgt gagccagctt atcaaccctc agcagcgcaa cgccctcact 1500 cctacaacca ttcctgatgg catgggagcc aacagatctg gcaagtctga aaatccctga 1560 gcaatttcga catgcgatct ggaagggcat cctggaccac cggcagctcc acgaattctc 1620 ctccccttct catctcctgc ggaccccaag cagtgcctct acagtcagtg tgggctccag 1680 tgagaccegg ggtgagegtg ttattgatge tgtgegatte acceteegee agaccatete 1740 tttcccaccc cgagatgagt ggaatgactt caactttgac atggatgctc gccgcaataa 1800 gcaacagcgc atcaaagagg agggggagtg agcctcacca tgtgagctct tcctatccct 1860

#### 238/299

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Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser 35 40 45

Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala 50 55 60

Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro 65 70 75 80

His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala 85 90 95

Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
100 105 110

Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly 115 120 125

Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr 130 135 140

Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn 165 170 175

Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val

Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val 195 200 205

Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg 210 215 220

Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val 225 230 235 240

Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg 245 250 255

239/299

Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp 260 265 270

Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr 275 280 285

His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp 290 295 300

Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu 305 310 315 320

Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His
325 330 335

Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu 340 345 350

Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser 355 360 365

Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val 370 380

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Ile Pro Asp Gly Met Gly Ala Asn Arg Ser Gly Lys Ser Glu Asn Pro 405 410 415

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<211> 461

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<400> 288

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Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
35 40 45

Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala 50 55 60

Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro 65 70 75 80

#### 240/299

His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala 105 Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn 150 Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn 170 Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val 185 Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val 200 Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg 210 215 Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val 230 Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg 245 250 Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln His Gln His Leu 345 Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val 375

241/299

Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr 385 390 395 400

Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met 405 410 415

Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro 420 425 430

Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro 435 440 445

Tyr Pro Thr Asp Cys Ser Ile Val Gly Ile Trp Gln Val 450 455 460

<210> 289

<400> 289 000

<210> 290

<211> 586

<212> PRT

<213> Homo sapiens

<400> 290

Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln 1 5 10 15

Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn 20 25 30

Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser 35 40 45

Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala 50 55 60

Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro 65 70 75 80

His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala 85 90 95

Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
100 105 110

Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Gln Gly
115 120 125

Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr 130 140

Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn 145 150 155 160

#### 242/299

Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val 185 Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val 200 Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val 230 235 Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp 265 Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr 280 His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp 295 Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln His Gln His Leu Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser 360 Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val 375 Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met 405 410 Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro 425 Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro 440 Tyr Pro Thr Asp Cys Ser Ile Val Gly Phe Leu Ala Arg Leu Gly Cys 455 Ser Ser Cys Leu Asp Tyr Phe Thr Thr Gln Gly Leu Thr Thr Ile Tyr

243/299 470 480 465 475 Gln Ile Glu His Tyr Ser Met Asp Asp Leu Ala Ser Leu Lys Ile Pro 485 490 Glu Gln Phe Arg His Ala Ile Trp Lys Gly Ile Leu Asp His Arg Gln Leu His Glu Phe Ser Ser Pro Ser His Leu Leu Arg Thr Pro Ser Ser Ala Ser Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val Ile Asp Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro Arg Asp Glu Trp Asn Asp Phe Asn Phe Asp Met Asp Ala Arg Arg Asn 565 570 Lys Gln Gln Arg Ile Lys Glu Glu Gly Glu 580 <210> 291 <400> 291 000 <210> 292 <211> 393 <212> PRT <213> Homo sapiens <400> 292 Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala

Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala 50 55 60

Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro 65 70 75 80

His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala

Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala 100 105 110

90

Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly

## 244/299

115 120 125 Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr 135 Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn 155 150 Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn 170 Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val 230 Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr 280 His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp 295 Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu 315 Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln His Gln His Leu Leu Gln Lys His Leu Leu Ser Ala Cys Phe Arg Asn Glu Leu Val Glu Pro Arg Arg Glu Thr Pro Lys Gln Ser Asp Val Phe Phe Arg His Ser 375 380 Lys Pro Pro Asn Arg Ser Val Tyr Pro 385 390 <210> 293

<400> 293

000

245/299

<210> 294 <211> 471 <212> PRT <213> Homo sapiens <400> 294 Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn 90 Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln 105 Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His 200 Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro 230 Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val 245 250 Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser

265

260

246/299

Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu 275 280 285

Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg 290 295 300

Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile 305 310 315 320

Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys 325 330 335

Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys 340 345 350

Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly 355 360 365

Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu 370 375 380

Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln 385 390 395 400

Gln Gln His Gln His Leu Leu Gln Lys Gln Thr Ser Ile Gln Ser 405 410 415

Pro Ser Ser Tyr Gly Asn Ser Ser Pro Pro Leu Asn Lys Met Asn Ser 420 425 430

Met Asn Lys Leu Pro Ser Val Ser Gln Leu Ile Asn Pro Gln Gln Arg
435 440 445

Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Arg 450 455 460

Ser Gly Lys Ser Glu Asn Pro 465 470

<210> 295

<400> 295

<210> 296

<211> 516

<212> PRT

<213> Homo sapiens

<400> 296

Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe 1 5 10 15

Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro
20 25 30

247/299

Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser 120 Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln 135 Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val 165 170 Met Thr Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr 185 Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His 195 200 205 Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys 330

248/299

Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys 340 345 350

Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly 355 360 365

Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu 370 375 380

Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln 385 390 395 400

Gln Gln His Gln His Leu Leu Gln Lys Gln Thr Ser Ile Gln Ser 405 410 415

Pro Ser Ser Tyr Gly Asn Ser Ser Pro Pro Leu Asn Lys Met Asn Ser 420 425 430

Met Asn Lys Leu Pro Ser Val Ser Gln Leu Ile Asn Pro Gln Gln Arg 435 440 445

Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Ile 450 455 460

Pro Met Met Gly Thr His Met Pro Met Ala Gly Asp Met Asn Gly Leu 465 470 475 480

Ser Pro Thr Gln Ala Leu Pro Pro Pro Leu Ser Met Pro Ser Thr Ser 485 490 495

His Cys Thr Pro Pro Pro Pro Tyr Pro Thr Asp Cys Ser Ile Val Gly 500 505 510

Ile Trp Gln Val 515

<210> 297

<400> 297 000

<210> 298

<211> 641

<212> PRT

<213> Homo sapiens

<400> 298

Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe 1 5 10 15

Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro 20 25 30

Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn 35 40 45

# 249/299

Lys	Ile 50	Glu	Ile	Ser	Met	Asp 55	Сув	Ile	Arg	Met	Gln 60	Asp	Ser	Asp	Leu
Ser 65	Asp	Pro	Met	Trp	Pro 70	Gln	Tyr	Thr	Asn	Leu 75	Gly	Leu	Leu	Asn	Ser 80
Met	Asp	Gln	Gln	Ile 85	Gln	Asn	Gly	Ser	Ser 90	Ser	Thr	Ser	Pro	Tyr 95	Asn
Thr	Asp	His	Ala 100	Gln	Asn	Ser	Val	Thr 105	Ala	Pro	Ser	Pro	Tyr 110	Ala	Gln
Pro	Ser	Ser 115	Thr	Phe	Asp	Ala	Leu 120	Ser	Pro	Ser	Pro	Ala 125	Ile	Pro	Ser
Asn	Thr 130	Asp	Tyr	Pro	Gly	Pro 135	His	Ser	Phe	Asp	Val 140	Ser	Phe	Gln	Gln
Ser 145	Ser	Thr	Ala	Lys	Ser 150	Ala	Thr	Trp	Thr	Tyr 155	Ser	Thr	Glu	Leu	Lys 160
Lys	Leu	Tyr	Cys	Gln 165	Ile	Ala	Lys	Thr	Cys 170	Pro	Ile	Gln	Ile	Lys 175	Val
Met	Thr	Pro	Pro 180	Pro	Gln	Gly	Ala	Val 185	Ile	Arg	Ala	Met	Pro 190	Val	Tyr
Lys	Lys	Ala 195	Glu	His	Val	Thr	Glu 200	Val	Val	Lys	Arg	Cys 205	Pro	Asn	His
Glu	Leu 210	Ser	Arg	Glu	Phe	Asn 215	Glu	Gly	Gln	Ile	Ala 220	Pro	Pro	Ser	His
Leu 225	Ile	Arg	Val	Glu	Gly 230	Asn	Ser	His	Ala	Gln 235	Tyr	Val	Glu	Asp	Pro 240
Ile	Thr	Gly	Arg	Gln 245	Ser	Val	Leu	Val	Pro 250	Tyr	Glu	Pro	Pro	Gln 255	Val
Gly	Thr	Glu	Phe 260	Thr	Thr	Val	Leu	Tyr 265	Asn	Phe	Met	Cys	Asn 270	Ser	Ser
Cys	Val	Gly 275	Gly	Met	Asn	Arg	Arg 280	Pro	Ile	Leu	Ile	Ile 285	Val	Thr	Leu
Glu	Thr 290	Arg	Asp	Gly	Gln	Val 295	Leu	Gly	Arg	Arg	Cys	Phe	Glu	Ala	Arg
Ile 305	Сув	Ala	Cys	Pro	Gly 310	Arg	Asp	Arg	Lys	Ala 315	Asp	Glu	Asp	Ser	Ile 320
Arg	Lys	Gln	Gln	Val 325	Ser	Asp	Ser	Thr	Lys 330	Asn	Gly	Asp	Gly	Thr 335	Lys
Arg	Pro	Phe	Arg 340	Gln	Asn	Thr	His	Gly 345	Ile	Gln	Met	Thr	Ser 350	Ile	Lys
Lys	Arg	Arg	Ser	Pro	Asp	Asp	Glu	Leu	Leu	Tyr	Leu	Pro	Val	Arg	Gly

250/299

								20 0, 200							
		355					360					365			
Arg	Glu 370	Thr	Tyr	Glu	Met	Leu 375	Leu	Lys	Ile	Lys	Glu 380	Ser	Leu	Glu	Leu
Met 385	Gln	Tyr	Leu	Pro	Gln 390	His	Thr	Ile	Glu	Thr 395	Tyr	Arg	Gln	Gln	Gln 400
Gln	Gln	Gln	His	Gln 405	His	Leu	Leu	Gln	Lys 410	Gln	Thr	Ser	Ile	Gln 415	Ser
Pro	Ser	Ser	Tyr 420	Gly	Asn	ser	ser	Pro 425	Pro	Leu	Asn	Lys	Met 430	Asn	Ser
Met	Asn	Lys 435	Leu	Pro	Ser	Val	Ser 440	Gln	Leu	Ile	Asn	Pro 445	Gln	Gln	Arg
Asn	Ala 450	Leu	Thr	Pro	Thr	Thr 455	Ile	Pro	Asp	Gly	Met 460	Gly	Ala	Asn	Ile
Pro 465	Met	Met	Gly	Thr	His 470	Met	Pro	Met	Ala	Gly 475	Asp	Met	Asn	Gly	Leu 480
Ser	Pro	Thr	Gln	Ala 485	Leu	Pro	Pro	Pro	Leu 490	Ser	Met	Pro	Ser	Thr 495	Ser
His	Cys	Thr	Pro 500	Pro	Pro	Pro	Tyr	Pro 505	Thr	Asp	Cys	Ser	Ile 510	Val	Gly
Phe	Leu	Ala 515	Arg	Leu	Gly	Cys	Ser 520	Ser	Сув	Leu	Asp	Tyr 525	Phe	Thr	Thr
Gln	Gly 530	Leu	Thr	Thr	Ile	Tyr 535	Gln	Ile	Glu	His	Tyr 540	Ser	Met	Asp	Asp
Leu 545	Ala	Ser	Leu	Lys	Ile 550	Pro	Glu	Gln	Phe	Arg 555	His	Ala	Ile	Trp	Lys 560
Gly	Ile	Leu	Asp	His 565	Arg	Gln	Leu	His	Glu 570	Phe	Ser	Ser	Pro	Ser 575	His
Leu	Leu	Arg	Thr 580	Pro	Ser	Ser	Ala	Ser 585	Thr	Val	Ser	Val	Gly 590	Ser	Ser
Glu	Thr	Arg 595	Gly	Glu	Arg	Val	Ile 600	Asp	Ala	Val	Arg	Phe 605	Thr	Leu	Arg
Gln	Thr 610	Ile	Ser	Phe	Pro	Pro 615	Arg	Asp	Glu	Trp	Asn 620	Asp	Phe	Asn	Phe
Asp 625	Met	Asp	Ala	Arg	Arg 630	Asn	Lys	Gln	Gln	Arg 635	Ile	Lys	Glu	Glu	Gly 640
Glu															

<210> 299

251/299

<400> 299 000

<210> 300

<211> 448

<212> PRT

<213> Homo sapiens

<400> 300

Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe 1 5 10 15

Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro 20 25 30

Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn 35 40 45

Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu
50 60

Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser 65 70 75 80

Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn 85 90 95

Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln
100 105 110

Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser 115 120 125

Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln 130 135 140

Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys 145 150 155 160

Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val 165 170 175

Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr 180 185 190

Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His 195 200 205

Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His 210 215 220

Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro 225 230 235 240

Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val
245 250 255

252/299

Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser 260 265 270

Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu 275 280 285

Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg 290 295 300

Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile 305 310 315

Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys 325 330 335

Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys 340 345 350

Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly 355 360 365

Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu 370 375 380

Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln 385 390 395 400

Gln Gln Gln His Gln His Leu Leu Gln Lys His Leu Leu Ser Ala Cys 405 410 415

Phe Arg Asn Glu Leu Val Glu Pro Arg Arg Glu Thr Pro Lys Gln Ser 420 425 430

Asp Val Phe Phe Arg His Ser Lys Pro Pro Asn Arg Ser Val Tyr Pro
435 440 445

<210> 301

<400> 301

000

<210> 302

<211> 461

<212> PRT

<213> Homo sapiens

<400> 302

Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln
1 5 10 15

Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn 20 25 30

Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser 35 40 45

253/299

Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala 85 90 Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala 105 Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly 120 Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn 150 155 Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn 170 Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val 185 Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg 215 Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg 250 Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His 325 330 Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln His Gln His Leu 345 Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser

254/299

360 355 Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val 375 Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr 385 390 395 Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met 405 410 Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro 420 425 Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro 440 Tyr Pro Thr Asp Cys Ser Ile Val Arg Ile Trp Gln Val <210> 303 <211> 1386 <212> DNA <213> Homo sapiens <400> 303 atgttgtacc tggaaaacaa tgcccagact caatttagtg agccacagta cacgaacctg 60 gggctcctga acagcatgga ccagcagatt cagaacggct cctcgtccac cagtccctat 120 aacacagacc acgcgcagaa cagcgtcacg gcgccctcgc cctacgcaca gcccagctcc 180 accttcgatg ctctctctcc atcacccgcc atcccctcca acaccgacta cccaggcccg 240 cacagtttcg acgtgtcctt ccaccagtcg agcaccgcca agtcggccac ctggacgtat 300 tccactgaac tgaagaaact ctactgccaa attgcaaaga catgccccat ccagatcaag 360 gtgatgaccc cacctcctca gggagctgtt atccgcgcca tgcctgtcta caaaaaagct 420 gagcacgtca cggaggtggt gaagcggtgc cccaaccatg agctgagccg tgaattcaac 480 gagggacaga ttgcccctcc tagtcatttg attcgagtag aggggaacag ccatgcccag 540 tatgtagaag atcccatcac aggaagacag agtgtgctgg taccttatga gccaccccag 600 qttggcactg aattcacgac agtcttgtac aatttcatgt gtaacagcag ttgtgttgga 660 gggatgaacc gccgtccaat tttaatcatt gttactctgg aaaccagaga tgggcaagtc 720 ctgggccgac gctgctttga ggcccggatc tgtgcttgcc caggaagaga caggaaggcg 780 gatgaagata gcatcagaaa gcagcaagtt tcggacagta caaagaacgg tgatggtacg 840 aagegeeegt ttegteagaa cacacatggt atecagatga catecateaa gaaacgaaga 900 tccccagatg atgaactgtt atacttacca gtgaggggcc gtgagactta tgaaatgctg 960 ttgaagatca aagagtccct ggaactcatg cagtaccttc ctcagcacac aattgaaacg 1020 tacaqqcaac aqcaacaqca qcaqcaccaq cacttacttc aqaaacaqac ctcaatacag 1080 tctccatctt catatqqtaa caqctcccca cctctgaaca aaatqaacaq catgaacaag 1140 etgeettetg tgagecaget tateaaceet cageagegea aegeeeteae teetacaace 1200 attectgatg geatgggage caacattece atgatgggea eccacatgee aatggetgga 1260 gacatgaatg gactcagccc cacccaggca ctccctcccc cactctccat gccatccacc 1320 teccaetgea caececeace tecqtatece acagattgea geattqteaq gatetggeaa 1380 gtctga 1386 <210> 304 <211> 393

<212> PRT

<213> Homo sapiens

## 255/299

<400> 304

Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln  $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ 

Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn 20 25 30

Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser 35 40 45

Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala 50 55 60

Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro 65 70 75 80

His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala  $85 \\ 90 \\ 95$ 

Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
100 105 110

Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly 115 120 125

Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr 130 135 140

Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn 145 150 155 160

Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn
165 170 175

Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val

Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val

Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg 210 215 220

Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val 225 230 235 240

Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg 245 250 255

Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp 260 265

Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr

His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp 290 295 300

256/299

Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu 315 Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His 325 Thr Ile Glu Thr Tyr Arq Gln Gln Gln Gln Gln His Gln His Leu Leu Gln Lys His Leu Leu Ser Ala Cys Phe Arg Asn Glu Leu Val Glu Pro Arg Arg Glu Thr Pro Lys Gln Ser Asp Val Phe Phe Arg His Ser Lys Pro Pro Asn Arg Ser Val Tyr Pro 390 <210> 305 <211> 1182 <212> DNA <213> Homo sapiens <400> 305 atgttgtacc tggaaaacaa tgcccagact caatttagtg agccacagta cacgaacctg 60 gggctcctga acagcatgga ccagcagatt cagaacggct cctcgtccac cagtccctat 120 aacacagacc acgcgcagaa cagcgtcacg gcgccctcgc cctacgcaca gcccagctcc 180 accttcgatg ctctctctc atcacccgcc atcccctcca acaccgacta cccaggcccg 240 cacagttteg acgtgteett ccagcagteg agcacegeca agteggecac etggacgtat 300 tccactgaac tgaaqaaact ctactgccaa attgcaaaga catgccccat ccagatcaag 360 gtgatgaccc cacctcctca gggagctgtt atccgcgcca tgcctgtcta caaaaaagct 420 gagcacgtca cggaggtggt gaagcggtgc cccaaccatg agctgagccg tgaattcaac 480 gagggacaga ttgcccctcc tagtcatttg attcgagtag aggggaacag ccatgcccag 540 tatgtagaag atcccatcac aggaagacag agtgtgctgg taccttatga gccaccccag 600 gttggcactg aattcacgac agtcttgtac aatttcatgt gtaacagcag ttgtgttgga 660 gggatgaacc gccgtccaat tttaatcatt gttactctgg aaaccagaga tgggcaagtc 720 ctgggccgac gctgctttga ggcccggatc tgtgcttgcc caggaagaga caggaaggcg 780 gatgaagata gcatcagaaa gcagcaagtt tcggacagta caaagaacgg tgatggtacg 840 aagegeeegt ttegteagaa cacacatggt atecagatga catecateaa gaaacgaaga 900 tccccagatg atgaactgtt atacttacca gtgaggggcc gtgagactta tgaaatgctg 960 ttgaagatca aagagtccct ggaactcatg cagtaccttc ctcagcacac aattgaaacg 1020 tacaggcaac agcaacagca gcagcaccag cacttacttc agaaacatct cctttcagcc 1080 tgcttcagga atgagcttgt ggagccccgg agagaaactc caaaacaatc tgacgtcttc 1140 tttagacatt ccaagccccc aaaccgatca gtgtacccat ag 1182 <210> 306 <211> 586 <212> PRT <213> Homo sapiens <400> 306 Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln 10 Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn 25 20

#### 257/299

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258/299

Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu 340 345 350

Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser 355 360 365

Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val 370 375 380

Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr 385 390 395 400

Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met 405 410 415

Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro 420 425 430

Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro 435 440 445

Tyr Pro Thr Asp Cys Ser Ile Val Ser Phe Leu Ala Arg Leu Gly Cys 450 455 460

Ser Ser Cys Leu Asp Tyr Phe Thr Thr Gln Gly Leu Thr Thr Ile Tyr 465 470 475 480

Gln Ile Glu His Tyr Ser Met Asp Asp Leu Ala Ser Leu Lys Ile Pro 485 490 495

Glu Gln Phe Arg His Ala Ile Trp Lys Gly Ile Leu Asp His Arg Gln 500 505 510

Leu His Glu Phe Ser Ser Pro Ser His Leu Leu Arg Thr Pro Ser Ser 515 520 525

Ala Ser Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val 530 540

Ile Asp Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro 545 550 555

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## 259/299

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	tcca	ctga	ac t	gaag	gaaac	t ct	acto	gccaa	ı att	gcaa	aga	cato	gccc	at o	ccaga	ıtcaag	360
	gtga	tgac	cc c	cacct	cato	a gg	gago	tgtt	: atc	atccgcgcca			tgto	ta d	caaaa	420	
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	1				5					10					15		
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	Gln	His	IIe	Trp	Asp	Phe	Leu	GLu		Pro	тте	Cys	Ser		GIn	Pro	
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		_		_	1		_		_	_	~ 7	_	~-		-m1	-	
	TTe	Asp		Asn	Pne	var	Asp		Pro	ser	GIU	Asp		Ата	Thr	Asn	
			35					40					45				
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	Lys		Glu	Ile	Ser	Met	Asp	Cys	Ile	Arg	Met		Asp	Ser	Asp	Leu	
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	Met	Asp	Gln	Gln	Ile	Gln	Asn	Gly	Ser	Ser	Ser	Thr	Ser	Pro	Tyr	Asn	
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100 105 110

Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser 115 120 125

260/299

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Lys	Leu	Tyr	Cys	Gln 165	Ile	Ala	Lys	Thr	Cys 170	Pro	Ile	Gln	Ile	Lys 175	Val
Met	Thr	Pro	Pro 180	Pro	Gln	Gly	Ala	Val 185	Ile	Arg	Ala	Met	Pro 190	Val	Tyr
Lys	Lys	Ala 195	Glu	His	Val	Thr	Glu 200	Val	Val	Lys	Arg	Cys 205	Pro	Asn	His
Glu	Leu 210	Ser	Arg	Glu	Phe	Asn 215	Glu	Gly	Gln	Ile	Ala 220	Pro	Pro	Ser	His
Leu 225	Ile	Arg	Val	Glu	Gly 230	Asn	Ser	His	Ala	Gln 235	Tyr	Val	Glu	Asp	Pro 240
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Gly	Thr	Glu	Phe 260	Thr	Thr	Val	Leu	Tyr 265	Asn	Phe	Met	Cys	Asn 270	Ser	Ser
Cys	Val	Gly 275	Gly	Met	Asn	Arg	Arg 280	Pro	Ile	Leu	Ile	Ile 285	Val	Thr	Leu
Glu	Thr 290	Arg	Asp	Gly	Gln	Val 295	Leu	Gly	Arg	Arg	Cys 300	Phe	Glu	Ala	Arg
Ile 305	Cys	Ala	Cys	Pro	Gly 310	Arg	Asp	Arg	Lys	Ala 315	Asp	Glu	Asp	Ser	Ile 320
Arg	Lys	Gln	Gln	Val 325	Ser	Asp	Ser	Thr	Lys 330	Asn	Gly	Asp	Gly	Thr 335	Lys
Arg	Pro	Phe	Arg 340	Gln	Asn	Thr	His	Gly 345	Ile	Gln	Met	Thr	Ser 350	Ile	Lys
Lys	Arg	Arg 355	Ser	Pro	Asp	Asp	Glu 360	Leu	Leu	Tyr	Leu	Pro 365	Val	Arg	Gly
Arg	Glu 370	Thr	Tyr	Glu	Met	Leu 375	Leu	Lys	Ile	Lys	Glu 380	Ser	Leu	Glu	Leu
Met 385	Gln	Tyr	Leu	Pro	Gln 390	His	Thr	Ile	Glu	Thr 395	Tyr	Arg	Gln	Gln	Gln 400
Gln	Gln	Gln	His	Gln 405	His	Leu	Leu	Gln	Lys 410	Gln	Thr	Ser	Ile	Gln 415	Ser
Pro	Ser	Ser	Tyr 420	Gly	Asn	Ser	Ser	Pro 425	Pro	Leu	Asn	Lys	Met 430	Asn	Ser

### 261/299

Met Asn Lys Leu Pro Ser Val Ser Gln Leu Ile Asn Pro Gln Gln Arg 435 440 Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Ile 455 Pro Met Met Gly Thr His Met Pro Met Ala Gly Asp Met Asn Gly Leu 470 Ser Pro Thr Gln Ala Leu Pro Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro Tyr Pro Thr Asp Cys Ser Ile Val Arg 505 Ile Trp Gln Val 515 <210> 309 <211> 1551 <212> DNA <213> Homo sapiens <400> 309 atgtcccaga gcacacagac aaatgaattc ctcagtccag aggttttcca gcatatctgq 60 gattttctgg aacagcctat atgttcagtt cagcccattg acttgaactt tgtggatgaa 120 ccatcagaag atggtgcgac aaacaagatt gagattagca tggactgtat ccgcatgcag 180 gacteggace tgagtgacee catgtggeca cagtacaega acetgggget cetgaacage 240 atggaccage agattcagaa eggeteeteg tecaccagte eetataacae agaccaegeg 300 cagaacagog teacggogoc etegecetac geacagocca getecacett egatgetete 360 totocatcac cogocatccc ctccaacacc qactacccaq gcccqcacaq tttcqacqtq 420 tecttecage agtegageae egecaagteg gecaeetgga egtattecae tgaaetgaag 480 aaactctact gccaaattgc aaagacatgc cccatccaga tcaaggtgat gaccccacct 540 cctcagggag ctgttatccg cgccatgcct gtctacaaaa aagctgagca cgtcacggag 600 gtggtgaagc ggtgccccaa ccatgagctg agccgtgaat tcaacgaggg acagattgcc 660 cctcctagtc atttgattcg agtagagggg aacagccatg cccagtatgt agaagatccc 720 atcacaggaa gacagagtgt gctggtacct tatgagccac cccaggttgg cactgaattc 780 acgacagtet tgtacaattt catgtgtaac agcagttgtg ttggagggat gaaccgccgt 840 ccaattttaa tcattgttac tctggaaacc agagatgggc aagtcctggg ccgacgctgc 900 tttgaggccc ggatctgtqc ttqcccagga agaqacagga agqcqqatqa aqataqcatc 960 agaaagcagc aagtttcgga cagtacaaag aacggtgatg gtacgaagcg cccgtttcgt 1020 cagaacacac atggtatcca gatgacatcc atcaagaaac gaagatcccc agatgatgaa 1080 ctgttatact taccagtgag gggccgtgag acttatgaaa tgctgttgaa gatcaaagag 1140 tccctggaac tcatgcagta ccttcctcag cacacaattg aaacgtacag gcaacagcaa 1200 cagcagcagc accagcactt acttcagaaa cagacctcaa tacagtctcc atcttcatat 1260 ggtaacagct ccccacctct gaacaaaatg aacagcatga acaagctgcc ttctgtgagc 1320 cagettatea acceteagea gegeaaegee eteacteeta caaceattee tgatggeatg 1380 ggagccaaca ttcccatgat gggcacccac atgccaatgg ctggagacat gaatggactc 1440 agccccaccc aggcactccc tececcactc tecatgccat ecacetecca etgcacacce 1500 ccacctccgt atcccacaga ttgcagcatt gtcaggatct ggcaagtctg a 1.551 <210> 310 <211> 641 <212> PRT

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262/299

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Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu 50 60

Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser 65 70 75 80

Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn 85 90 95

Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln
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Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser 115 120 125

Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln 130 135 140

Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys 145 150 155

Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val 165 170 175

Met Thr Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr 180 185 190

Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His 195 200 205

Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His 210 215 220

Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro 225 230 235 240

Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val
245 250 255

Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser 260 270

Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu 275 280 285

Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg 290 295 300

263/299

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Arg	Pro	Phe	Arg 340	Gln	Asn	Thr	His	Gly 345	Ile	Gln	Met	Thr	Ser 350	Ile	Lys
Lys	Arg	Arg 355	Ser	Pro	Asp	Asp	Glu 360	Leu	Leu	Tyr	Leu	Pro 365	Val	Arg	Gly
Arg	Glu 370	Thr	Tyr	Glu	Met	Leu 375	Leu	Lys	Ile	Lys	Glu 380	Ser	Leu	Glu	Leu
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Pro 465	Met	Met	Gly	Thr	His 470	Met	Pro	Met	Ala	Gly 475	Asp	Met	Asn	Gly	Leu 480
Ser	Pro	Thr	Gln	Ala 485	Leu	Pro	Pro	Pro	Leu 490	Ser	Met	Pro	Ser	Thr 495	Ser
His	Cys	Thr	Pro 500	Pro	Pro	Pro	Tyr	Pro 505	Thr	Asp	Cys	Ser	Ile 510	Val	Ser
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Glu	Thr	Arg 595	Gly	Glu	Arg	Val	Ile 600	Asp	Ala	Val	Arg	Phe 605	Thr	Leu	Arg
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264/299

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265/299

Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro 25 Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser 120 Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln 135 Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys 150 Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val 170 165 Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr 185 Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile

Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys

266/299 325 330 335 Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys 345 Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu 375 Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln 385 Gln Gln Gln His Gln His Leu Leu Gln Lys His Leu Leu Ser Ala Cys 405 410 Phe Arg Asn Glu Leu Val Glu Pro Arg Arg Glu Thr Pro Lys Gln Ser 420 425 Asp Val Phe Phe Arg His Ser Lys Pro Pro Asn Arg Ser Val Tyr Pro 440 <210> 313 <211> 2816 <212> DNA <213> Homo sapiens <400> 313 tcqttqatat caaaqacaqt tqaaqqaaat qaattttqaa acttcacqqt qtqccaccct 60

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267/299

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gaaaggggca ttaagatgtt tattggaacc cttttctgtc ttcttctgtt gtttttctaa 1860
aattcacagg gaagcttttg agcaggtctc aaacttaaga tgtcttttta agaaaaggag 1920
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ccettttaat gctggtcatg taataatatt gcaagtagta agaaacgaag gtgtcaagtg 2040
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ttaagataat agcataaaga ctttaaaaat gttcctcccc tccatcttcc cacacccagt 2700
caccagcact gtattttctg tcaccaagac aatgatttct tgttattgag gctgttgctt 2760
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<211> 499
<212> PRT
<213> Homo sapiens
<400> 314
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His Leu Trp Ser Ser Leu Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro
Gln Ser Ser Arg Gly Asn Asn Glu Val Val Gly Gly Thr Asp Ser Ser
Met Asp Val Phe His Leu Glu Gly Met Thr Thr Ser Val Met Ala Gln
Phe Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala
Ser Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His
Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala
            100
                                105
                                                    110
Pro Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu
                            120
Val Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr
    130
                        135
Ser Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro
145
                    150
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Ile Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg

268/299

165 170 175 Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Val Val Lys 180 185 Arg Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln 215 Tyr Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe 250 Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Ile Thr Leu Glu Met Arg Asp Gly Gln Val Leu Gly Arg Arg 280 Ser Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala 315 Lys Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Val Pro Ala Leu Gly Ala Gly Val Lys Lys Arg Arg His Gly Asp Glu Asp Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu Val Asp Ser Tyr Arg Gln Gln Gln Leu Leu Gln Arg Pro Ser 390 His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys 410 Val His Gly Gly Met Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly 425 Gln Pro Pro Pro His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val Gly Pro Gly Met Leu Asn Asn His Gly His Ala Val Pro Ala Asn Gly 455 Glu Met Ser Ser Ser His Ser Ala Gln Ser Met Val Ser Gly Ser His 465 470 475

269/299

Cys Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Arg Thr 485 490 495

Trp Gly Pro

<210> 315

<211> 636

<212> PRT

<213> Homo sapiens

<400> 315

Met Ala Gln Ser Thr Ala Thr Ser Pro Asp Gly Gly Thr Thr Phe Glu

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His Leu Trp Ser Ser Leu Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro 20 25 30

Gln Ser Ser Arg Gly Asn Asn Glu Val Val Gly Gly Thr Asp Ser Ser 35 40 45

Met Asp Val Phe His Leu Glu Gly Met Thr Thr Ser Val Met Ala Gln 50 55 60

Phe Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala 65 70 75 80

Ser Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His
85 90 95

Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala 100 105 110

Pro Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu 115 120 125

Val Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr 130 135 140

Ser Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro 145 150 155 160

Ile Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg
165 170 175

Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Val Lys 180 185 190

Arg Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser 195 200 205

Ala Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln 210 215 220

Tyr Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Pro Tyr 225 230 235 240

Glu	Pro	Pro	Gln	Val 245	Gly	Thr	Glu	Phe	Thr 250	Thr	Ile	Leu	Tyr	Asn 255	Phe
Met	Cys	Asn	Ser 260	Ser	Cys	Val	Gly	Gly 265	Met	Asn	Arg	Arg	Pro 270	Ile	Leu
Ile	Ile	Ile 275	Thr	Leu	Glu	Met	Arg 280	Asp	Gly	Gln	Val	Leu 285	Gly	Arg	Arg
Ser	Phe 290	Glu	Gly	Arg	Ile	Cys 295	Ala	Cys	Pro	Gly	Arg 300	Asp	Arg	Lys	Ala
Asp 305	Glu	Asp	His	Tyr	Arg 310	Glu	Gln	Gln	Ala	Leu 315	Asn	Glu	Ser	Ser	Ala 320
Lys	Asn	Gly	Ala	Ala 325	Ser	Lys	Arg	Ala	Phe 330	Lys	Gln	Ser	Pro	Pro 335	Ala
Val	Pro	Ala	Leu 340	Gly	Ala	Gly	Val	Lys 345	Lys	Arg	Arg	His	Gly 350	Asp	Glu
Asp	Thr	Tyr 355	Tyr	Leu	Gln	Val	Arg 360	Gly	Arg	Glu	Asn	Phe 365	Glu	Ile	Leu
Met	Lys 370	Leu	Lys	Glu	Ser	Leu 375	Glu	Leu	Met	Glu	Leu 380	Val	Pro	Gln	Pro
Leu 385	Val	Asp	Ser	Tyr	Arg 390	Gln	Gln	Gln	Gln	Leu 395	Leu	Gln	Arg	Pro	Ser 400
His	Leu	Gln	Pro	Pro 405	Ser	Tyr	Gly <sub>.</sub>	Pro	Val 410	Leu	Ser	Pro	Met	Asn 415	Lys
Val	His	Gly	Gly 420	Met	Asn	Lys	Leu	Pro 425	Ser	Val	Asn	Gln	Leu 430	Val	Gly
Gln	Pro	Pro 435	Pro	His	Ser	Ser	Ala 440	Ala	Thr	Pro	Asn	Leu 445	Gly	Pro	Val
Gly	Pro 450	Gly	Met	Leu	Asn	Asn 455	His	Gly	His	Ala	Val 460	Pro	Ala	Asn	Gly
Glu 465	Met	Ser	Ser	Ser	His 470	Ser	Ala	Gln	Ser	Met 475	Val	Ser	Gly	Ser	His 480
Cys	Thr	Pro	Pro	Pro 485	Pro	Tyr	His	Ala	Asp 490	Pro	Ser	Leu	Val	Ser 495	Phe
Leu	Thr	Gly	Leu 500	Gly	Сув	Pro	Asn	Cys 505	Ile	Glu	Tyr	Phe	Thr 510	Ser	Gln
Gly	Leu	Gln 515	Ser	Ile	Tyr	His	Leu 520	Gln	Asn	Leu	Thr	Ile 525	Glu	Asp	Leu
Gly	Ala 530	Leu	Lys	Ile	Pro	Glu 535	Gln	Tyr	Arg	Met	Thr 540	Ile	Trp	Arg	Gly
Leu	Gln	Asp	Leu	Lys	Gln	Gly	His	Asp	Tyr	ser	Thr	Ala	Gln	Gln	Leu

271/299

545 550 555 560

Leu Arg Ser Ser Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu
565 570 575

Leu Gln Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg His
580 585 590

Thr Ile Thr Ile Pro Asn Arg Gly Gly Pro Gly Gly Pro Asp Glu
595 600 605

Trp Ala Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys Gln 610 615 620

Pro Ile Lys Glu Glu Phe Thr Glu Ala Glu Ile His 625 630 635

<210> 316

<211> 588

<212> PRT

<213> Homo sapiens

<400> 316

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Phe Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala 20 25 30

Ser Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His
35 40 45

Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala 50 60

Pro Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu 65 70 75 80

Val Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr 85 90 95

Ser Pro Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro 100 105 110

Ile Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg 115 120 125

Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Val Val Lys 130 135 140

Arg Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser 145 150 155

Ala Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln
165 170 175

Tyr Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr

272/299

180 185 190 Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe 200 Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Ile Thr Leu Glu Met Arg Asp Gly Gln Val Leu Gly Arg Arg Ser Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala Lys Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala 280 Val Pro Ala Leu Gly Ala Gly Val Lys Lys Arg Arg His Gly Asp Glu Asp Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu 310 315 Met Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro 330 Leu Val Asp Ser Tyr Arg Gln Gln Gln Leu Leu Gln Arg Pro Ser 340 345 His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys 360 Val His Gly Gly Met Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly Gln Pro Pro Pro His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val Gly Pro Gly Met Leu Asn Asn His Gly His Ala Val Pro Ala Asn Gly Glu Met Ser Ser Ser His Ser Ala Gln Ser Met Val Ser Gly Ser His Cys Thr Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Ser Phe Leu Thr Gly Leu Gly Cys Pro Asn Cys Ile Glu Tyr Phe Thr Ser Gln Gly Leu Gln Ser Ile Tyr His Leu Gln Asn Leu Thr Ile Glu Asp Leu 475 Gly Ala Leu Lys Ile Pro Glu Gln Tyr Arg Met Thr Ile Trp Arg Gly 490

273/299

Leu Gln Asp Leu Lys Gln Gly His Asp Tyr Ser Thr Ala Gln Gln Leu 500 505 Leu Arg Ser Ser Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu

520

Leu Gln Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg His

Thr Ile Thr Ile Pro Asn Arg Gly Gly Pro Gly Gly Pro Asp Glu 550

Trp Ala Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys Gln 570 565

Pro Ile Lys Glu Glu Phe Thr Glu Ala Glu Ile His 580 585

<210> 317

<211> 2234

<212> DNA

<213> Homo sapiens

<400> 317

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## 274/299

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<210> 318 <211> 732 <212> PRT <213> Homo sap	iens				
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Val Glu Thr Pi	e Ala Phe O	Gln Ala Glu 25		Gln Leu Met	
Ile Ile Asn Th	r Phe Tyr	Ser Asn Lys	s Glu Ile	Phe Leu Arg	Glu Leu
Ile Ser Asn Se	r Ser Asp	Ala Leu Ası 55	o Lys Ile	Arg Tyr Glu 60	Thr Leu
Thr Asp Pro Se	r Lys Leu 70	Asp Ser Gly	y Lys Glu 75	Leu His Ile	Asn Leu 80
Ile Pro Asn Ly	rs Gln Asp 85	Arg Thr Let	u Thr Ile 90	Val Asp Thr	Gly Ile 95
Gly Met Thr Ly	-	Leu Ile Ası 10		Gly Thr Ile	-
Ser Gly Thr Ly 115	rs Ala Phe	Met Glu Ala 120	a Leu Gln	Ala Gly Ala 125	Asp Ile
Ser Met Ile G	y Gln Phe	Gly Val Gly 135	y Phe Tyr	Ser Ala Tyr 140	Leu Val
Ala Glu Lys Va 145	l Thr Val 150	Ile Thr Lys	s His Asn 155	Asp Asp Glu	Gln Tyr 160
Ala Trp Glu Se	er Ser Ala 165	Gly Gly Se	r Phe Thr 170	Val Arg Thr	Asp Thr 175
Gly Glu Pro Me		Gly Thr Lys		Leu His Leu 190	<del>-</del>
Asp Gln Thr G	u Tyr Leu	Glu Glu Are	g Arg Ile	Lys Glu Ile 205	Val Lys
Lys His Ser G	n Phe Ile	Gly Tyr Pro	o Ile Thr	Leu Phe Val	Glu Lys
Glu Arg Asp Ly 225	rs Glu Val 230	Ser Asp As	p Glu Ala 235	Glu Glu Lys	Glu Asp 240

## 275/299

Lys Glu Glu Glu Lys Glu Lys Glu Lys Glu Ser Glu Asp Lys Pro Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Lys Lys Asp Gly 265 Asp Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile Thr Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp Glu Asp His Leu Ala Val Lys His Phe Ser Val Glu Gly Gln Leu Glu 330 Phe Arg Ala Leu Leu Phe Val Pro Arg Arg Ala Pro Phe Asp Leu Phe 340 Glu Asn Arg Lys Lys Lys Asn Asn Ile Lys Leu Tyr Val Arg Arg Val 360 Phe Ile Met Asp Asn Cys Glu Glu Leu Ile Pro Glu Tyr Leu Asn Phe 375 Ile Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn Ile Ser Arg 390 395 Glu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Leu Val Lys Lys Cys Leu Glu Leu Phe Thr Glu Leu Ala Glu Asp Lys Glu Asn Tyr Lys Lys Phe Tyr Glu Gln Phe Ser Lys Asn Ile Lys Leu Gly Ile His Glu Asp Ser Gln Asn Arg Lys Lys Leu Ser Glu Leu Leu Arg Tyr Tyr Thr Ser Ala Ser Gly Asp Glu Met Val Ser Leu Lys Asp Tyr Cys Thr Arg Met Lys Glu Asn Gln Lys His Ile Tyr Tyr Ile Thr Gly Glu Thr Lys Asp Gln Val Ala Asn Ser Ala Phe Val Glu Arg Leu Arg Lys His Gly Leu Glu Val Ile Tyr Met Ile Glu Pro Ile Asp Glu Tyr 520 Cys Val Gln Gln Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Ser Val 535

276/299

Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Glu Lys Lys 545

Glu Glu Glu Lys Lys Thr Lys Phe Glu Asn Leu Cys Lys Ile Met Lys

Asp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg Leu 580 595

Val Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala 595 600 605

Asn Met Glu Arg Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr 610 615 620

Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp His 625 630 635

Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp 645 650 655

Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu 660 665 670

Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg Ile 675 680 685

Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr 690 695 700

Ala Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu 705 710 715 720

Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp 725 730

<210> 319

<211> 249

<212> PRT

<213> Homo sapiens

<400> 319

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Glu Gln Val Ala Asn Ser Ala Phe Val Glu Arg Val Arg Lys Gln Gly 20 25 30

Phe Glu Val Val Tyr Met Thr Glu Pro Ile Asp Glu Tyr Cys Val Glu 35 40 45

Gln Leu Lys Glu Phe Asp Gly Lys Ser Leu Val Ser Val Thr Lys Glu
50 60

Gly Leu Glu Leu Pro Glu Asp Glu Glu Glu Lys Lys Lys Met Glu Glu 65 70 75 80

277/299

Ser Lys Glu Lys Phe Glu Asn Leu Cys Lys Leu Met Lys Glu Ile Leu 90

Asp Lys Lys Val Glu Lys Val Thr Ile Ser Asn Arg Leu Val Ser Ser 100

Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala Asn Met Glu 115 120 125

Gln Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr Met Gly Tyr 130 135 140

Met Met Ala Lys Lys His Leu Glu Ile Asn Pro Asp His Pro Ile Met 145 150 155 160

Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp Lys Ala Val
165 170 175

Lys Asp Leu Val Val Leu Leu Phe Glu Thr Ala Leu Leu Ser Ser Gly
180 185 190

Phe Ser Leu Glu Asp Pro Gln Thr His Ser Asn His Ile Tyr His Met 195 200 205

Ile Lys Leu Gly Leu Gly Thr Asp Glu Asp Glu Val Ala Ala Glu Glu 210 215 220

Pro Ser Asp Ala Val Pro Asp Glu Ile Pro Pro Leu Glu Gly Asp Glu 225 230 235 240

Asp Ala Ser Arg Met Glu Glu Val Asp 245

<210> 320

<211> 1313

<212> DNA

<213> Homo sapiens

<400> 320

tggtgtggtt gactctgagg atctgcccct gaacatctgc cgagagatgc tccagcagag 60 caaaatcttg aaagtcattc gcaaaaacat tgttaagaag tgccttgagc tcttctctga 120 gctggcagaa gacaaggaga ttataagaaa ttctatgagg cattttctaa aaatctcaag 180 cttggaatcc acgaagactc cactaaccgc caccgcctgt ctgagctgct gcgctgtcac 240 acctcccagt ctggagatga gatgacatct ctgtcgtagt atgtttctca catgaaggag 300 acacagaagt ccacctatta catcactggt gagagcaaag agcaggtggc caactctgct 360 tttgtggagc gagtgcggaa acagggcttc gaggtggtat atatgactga gcccattgac 420 gagtactgtg tgcagcagct caaggagttt gatgggaaaa gcctggtctc agttaccaag 480 gagggtctgg agctacctga ggatqaqqaq qaqaaqaaqa aqatggaaqa aaqcaaqgaa 540 aagtttgaga acctctgcaa gctcatgaaa gaaatcttag ataagaaggt tgagaaggtg 600 acaatctcca atagacttgt gtcttcaccc tgctgcattg tgaccagcac ctacggctgg 660 acagccaata tggagcagat catgaaagcc caggcacttc gggacaactc caccatgggc 720 tatatgatgg ccaaaaagca cctggagatc aaccccgacc accccatcat ggagacgctg 780 cggcagaagg ctgaggccga caagaatgat aaggcagtta aggacctggt ggtgctgctg 840 tttgaaaccg ccctgctatc ttcgggcttt tcccttgagg atccccagac ccactccaac 900 cacatctacc acatgatcaa gctaggtcta ggtactgatg aagatgaagt ggcagcagag 960 gaacccagtg atgcagttcc tgatgagatc ccccctcttg agggtgatga qqatgcgtct 1020 cgcatggaag aagtcgatta ggagttcata gttggaaaac ttgtgccctt gtatagtgtc 1080

### 278/299

cccatggctc ccactgcagc ctcgagtgcc cctgtcccac ctggctgctg gtgtctagtg 1140 ttttttccc tctcctgtcc ttgtgttgaa ggcaggaaac caagggtgtc aagccccatt 1200 ccctctctac tcttgacagc aggattggat gttgtgtatt gtggtttatt ttattttctt 1260 cattttgttc tgaaattaaa gaatgtaaaa taaagaatat gccgttttta tac 1313

<210> 321

<211> 724

<212> PRT

<213> Mus musculus

<400> 321

Met Pro Glu Glu Val His His Gly Glu Glu Glu Val Glu Thr Phe Ala 1 5 10 15

Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu Ile Ile Asn Thr Phe 20 25 30

Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser 35 40 45

Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Ser Lys 50 55 60

Leu Asp Ser Gly Lys Glu Leu Lys Ile Asp Ile Leu Pro Asn Pro Gln 65 70 75 80

Glu Arg Thr Leu Thr Leu Val Asp Thr Gly Ile Gly Met Thr Lys Ala 85 90 95

Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Lys Ala 100 105 110

Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile Ser Met Ile Gly Gln 115 120 125

Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Glu Lys Val Val 130 140

Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr Ala Trp Glu Ser Ser 145 150 155

Ala Gly Gly Ser Phe Thr Val Arg Ala Asp His Gly Glu Pro Ile Gly 165 170 175

Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu Asp Gln Thr Glu Tyr 180 185 190

Leu Glu Glu Arg Arg Val Lys Glu Val Val Lys Lys His Ser Gln Phe 195 200 205

Ile Gly Tyr Pro Ile Thr Leu Tyr Leu Glu Lys Glu Arg Glu Lys Glu 210 215 220

Ile Ser Asp Asp Glu Ala Glu Glu Lys Gly Glu Lys Glu Glu Glu 225 230 235 240

Asp Lys Glu Asp Glu Glu Lys Pro Lys Ile Glu Asp Val Gly Ser Asp

				245					250					255	
Glu	Glu	Asp	Asp 260	Ser	Gly	Lys	Asp	Lys 265	Lys	Lys	Lys	Thr	Lys 270	Lys	Ile
Lys	Glu	Lys 275	Tyr	Ile	Asp	Gln	Glu 280	Glu	Leu	Asn	Lys	Thr 285	Lys	Pro '	Ile
Trp	Thr 290	Arg	Asn	Pro	Asp	Asp 295	Ile	Thr	Gln	Glu	Glu 300	Tyr	Gly	Glu	Phe
Tyr 305	Lys	Ser	Leu	Thr	Asn 310	Asp	Trp	Glu	Asp	His 315	Leu	Ala	Val	Lys	His 320
Phe	Ser	Val	Glu	Gly 325	Gln	Leu	Glu	Phe	Arg 330	Ala	Phe	Leu	Phe	Ile 335	Pro
Arg	Arg	Ala	Pro 340	Phe	Asp	Leu	Phe	Glu 345	Asn	Lys	Lys	Lys	Lув 350	Asn	Asn
Ile	Lys	Leu 355	Tyr	Val	Arg	Arg	Val 360	Phe	Ile	Met	Asp	Ser 365	Cys	Asp	Glu
Leu	Ile 370	Pro	Glu	Tyr	Leu	Asn 375	Phe	Ile	Arg	Gly	Val 380	Val	Asp	Ser	Glu
Asp 385	Leu	Pro	Leu	Asn	Ile 390	Ser	Arg	Glu	Met	Leu 395	Gln	Gln	Ser	Lys	Ile 400
Leu	Lys	Val	Ile	Arg 405	Lys	Asn	Ile	Val	Lys 410	Lys	Cys	Leu	Glu	Leu 415	Phe
Ser	Glu	Leu	Ala 420	Glu	Asp	Lys	Glu	Asn 425	Tyr	Lys	Lys	Phe	Tyr 430	Glu	Ala
Phe	Ser	Lys 435	Asn	Leu	Lys	Leu	Gly 440	Ile	His	Glu	Asp	Ser 445	Thr	Asn	Arg
Arg	Arg 450	Leu	Ser	Glu	Leu	Leu 455	Arg	Tyr	His	Thr	Ser 460	Gln	Ser	Gly	Asp
Glu 465	Met	Thr	Ser	Leu	Ser 470	Glu	Tyr	Val	Ser	Arg 475	Met	Lys	Glu	Thr	Gln 480
Lys	Ser	Ile	Tyr	Tyr 485	Ile	Thr	Gly	Glu	Ser 490	Lys	Glu	Gln	Val	Ala 495	Asn
Pro	Ala	Phe	Val 500	Glu	Arg	Val	Arg	Lys 505	Arg	Gly	Phe	Glu	۷al 510	Val	Tyr
Met	Thr	Glu 515	Pro	Ile	Asp	Glu	Tyr 520	Cys	Val	Gln	Gln	Leu 525	Lys	Glu	Phe
Asp	Gly 530	Lys	Ser	Leu	Val	Ser 535	Val	Thr	Lys	Glu	Gly 540	Leu	Glu	Leu	Pro
Glu 545	Asp	Glu	Glu	Glu	Lуs 550	Lys	Lys	Met	Glu	Glu 555	Ser	Lys	Ala	Lys	Phe 560

280/299

Glu Asn Leu Cys Lys Leu Met Lys Glu Ile Leu Asp Lys Lys Val Glu
565 570 575

Lys Val Thr Ile Ser Asn Arg Leu Val Ser Ser Pro Cys Cys Ile Val 580 590

Thr Ser Thr Tyr Gly Trp Thr Ala Asn Met Glu Arg Ile Met Lys Ala 595 600 605

Gln Ala Leu Arg Asp Asn Ser Thr Met Gly Tyr Met Met Ala Lys Lys 610 615 620

His Leu Glu Ile Asn Pro Asp His Pro Ile Val Glu Thr Leu Arg Gln 625 630 635 640

Lys Ala Glu Ala Asp Lys Asn Asp Lys Ala Val Lys Asp Leu Val Val 645 650 655

Leu Leu Phe Glu Thr Ala Leu Leu Ser Ser Gly Phe Ser Leu Glu Asp
660 665 670

Pro Gln Thr His Ser Asn Arg Ile Tyr Arg Met Ile Lys Leu Gly Leu 675 680 685

Gly Ile Asp Glu Asp Glu Val Thr Ala Glu Glu Pro Ser Ala Ala Val 690 695 700

Pro Asp Glu Ile Pro Pro Leu Glu Gly Asp Glu Asp Ala Ser Arg Met 705 710 715 720

Glu Glu Val Asp

<210> 322

<211> 724

<212> PRT

<213> Rattus sp.

<400> 322

Met Pro Glu Glu Val His His Gly Glu Glu Glu Val Glu Thr Phe Ala 1 5 10 15

Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu Ile Ile Asn Thr Phe 20 25 30

Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser

Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Ser Lys 50 55 60

Leu Asp Ser Gly Lys Glu Leu Lys Ile Asp Ile Ile Pro Asn Pro Gln 65 70 75 80

Glu Ala Thr Leu Thr Leu Val Asp Thr Gly Ile Gly Met Thr Lys Ala 85 90 95

281/299

Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Lys Ala 105 Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile Ser Met Ile Gly Gln 120 Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Glu Lys Val Val 135 Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr Ala Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Ala Asp His Gly Glu Pro Ile Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu Asp Gln Thr Glu Tyr Leu Glu Glu Arg Arg Val Lys Glu Val Val Lys Lys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Tyr Leu Glu Lys Glu Arg Glu Lys Glu Ile Ser Asp Asp Glu Ala Glu Glu Glu Lys Gly Glu Lys Glu Glu Asp Lys Glu Asp Glu Glu Lys Pro Lys Ile Glu Asp Val Gly Ser Asp Glu Glu Asp Asp Ser Gly Lys Asp Lys Lys Lys Lys Thr Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu Leu Asn Lys Thr Lys Pro Ile 280 285 Trp Thr Arg Asn Pro Asp Asp Ile Thr Gln Glu Glu Tyr Gly Glu Phe 295 Tyr Lys Ser Leu Thr Asn Asp Trp Glu Asp His Leu Ala Val Lys His 305 310 315 Phe Ser Val Glu Gly Gln Leu Glu Phe Arg Ala Leu Leu Phe Ile Pro Arg Arg Ala Pro Phe Asp Leu Phe Glu Asn Lys Lys Lys Asn Asn Ile Lys Leu Tyr Val Arg Arg Val Phe Ile Met Asp Ser Cys Asp Asp Leu Ile Pro Glu Tyr Leu Asn Phe Ile Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn Ile Ser Arg Glu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Ile Val Lys Lys Cys Leu Glu Leu Phe

282/299

405 415 410 Ser Glu Leu Ala Glu Asp Lys Glu Asn Tyr Lys Lys Phe Tyr Glu Ala 425 Phe Ser Lys Asn Leu Lys Leu Gly Ile His Glu Asp Ser Thr Asn Arg Arg Arg Leu Ser Glu Leu Leu Arg Tyr His Thr Ser Gln Ser Gly Asp Glu Met Thr Ser Leu Ser Glu Tyr Val Ser Arg Met Lys Glu Thr Gln Lys Ser Ile Tyr Tyr Ile Thr Gly Glu Ser Lys Glu Gln Val Ala Asn Ser Ala Phe Val Glu Arg Val Arg Lys Arg Gly Phe Glu Val Val Tyr 505 Met Thr Glu Pro Ile Asp Glu Tyr Cys Val Gln Gln Leu Lys Glu Phe 520 Asp Gly Lys Ser Leu Val Ser Val Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Lys Lys Lys Met Glu Glu Ser Lys Ala Arg Phe 550 Glu Asn Leu Cys Lys Leu Met Lys Glu Ile Leu Asp Lys Lys Val Glu 565 570 Lys Val Thr Ile Ser Asn Arg Leu Val Ser Ser Pro Cys Cys Ile Val 585 Thr Ser Thr Tyr Gly Trp Thr Ala Asn Met Glu Arg Ile Met Lys Ala 600 Gln Ala Leu Arg Asp Asn Ser Thr Met Gly Tyr Met Met Ala Lys Lys His Leu Glu Ile Asn Pro Asp His Pro Ile Val Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp Lys Ala Val Lys Asp Leu Val Val Leu Leu Phe Glu Thr Ala Leu Ser Ser Leu Ala Ser His Phe Arg Arg Pro Lys Thr His Ser Asn Arg Ile Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Glu Val Thr Ala Glu Glu Pro Ser Ala Ala Val Pro Asp Glu Ile Pro Pro Leu Glu Gly Asp Glu Asp Ala Ser Arg Met 710

### 283/299

Glu Glu Val Asp

<210> 323

<211> 733

<212> PRT

<213> Cricetulus griseus

<400> 323

Met Pro Glu Glu Thr Gln Thr Gln Asp Gln Pro Met Glu Glu Glu 1 5 10 15

Val Glu Thr Phe Ala Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu 20 25 30

Ile Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu
35 40 45

Ile Ser Asn Ser Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu 50 55 60

Thr Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Ile 65 70 75 80

Ile Pro Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Asp Thr Gly Ile
85 90 95

Gly Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys 100 105 110

Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile 115 120 125

Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Thr Ala Tyr Leu Val 130 135 140

Ala Glu Lys Val Thr Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr 145 150 155 160

Ala Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Thr Asp Thr 165 170 175

Gly Glu Pro Met Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu
180 185 190

Asp Gln Thr Glu Tyr Met Glu Glu Arg Arg Ile Lys Glu Ile Val Lys 195 200 205

Lys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Phe Val Glu Lys 210 220

Glu Arg Asp Lys Glu Val Ser Asp Asp Glu Ala Glu Glu Lys Glu Asp 225 230 235 240

Lys Glu Glu Glu Lys Glu Lys Glu Lys Gly Ile Asp Asp Lys Pro 245 250 255

Glu	Ile	Glu	Asp 260	Val	Gly	Ser	Asp	Glu 265	Glu	Glu	Glu	Glu	Lys 270	Lys	Asp
Gly	Asp	Lys 275	Lys	Lys	Lys	Lys	Lуs 280	Ile	Lys	Glu	Lys	Tyr 285	Ile	Asp	Gln
Glu	Glu 290	Leu	Asn	Lys	Thr	Lys 295	Pro	Ile	Trp	Thr	Arg 300	Asn	Pro	Asp	Asp
Ile 305	Thr	Asn	Glu	Glu	Tyr 310	Gly	Glu	Phe	Tyr	Lys 315	Ser	Leu	Thr	Asn ·	Asp 320
Trp	Glu	Glu	His	Leu 325	Ala	Val	Lys	His	Phe 330	Ser	Val	Glu	Gly	Gln 335	Leu
Glu	Phe	Arg	Ala 340	Leu	Leu	Phe	Val	Pro 345	Arg	Arg	Ala	Pro	Phe 350	qaA	Leu
Phe	Glu	Asn 355	Arg	Lys	Lys	Lys	Asn 360	Asn	Ile	Lys	Leu	Tyr 365	Val	Arg	Arg
Val	Phe 370	Ile	Met	Asp	Asn	Cys 375	Glu	Glu	Leu	Phe	Pro 380	Glu	Tyr	Leu	Asn
Phe 385	Ile	Arg	Gly	Val	Val 390	Asp	Ser	Glu	Asp	Leu 395	Pro	Leu	Asn	Ile	Ser 400
Arg	Glu	Ile	Leu	Gln 405	Gln	Ser	Lys	Ile	Leu 410	Ъуs	Val	Ile	Arg	Lys 415	Asn
Leu	Val	Arg	Lуs 420	Cys	Leu	Glu	Leu	Phe 425	His	Glu	Leu	Ala	Glu 430	Asp	Lys
Glu	Asn	Tyr 435	Lys	Lys	Phe	Tyr	Glu 440	Gln	Phe	Ser	Lys	Asn 445	Ile	Lys	Leu
Gly	Ile 450	His	Glu	Asp	Ser	Gln 455	Asn	Arg	Lys	Lys	Leu 460	Ser	Glu	Leu	Leu
Arg 465	Tyr	Tyr	Thr	Ser	Ala 470	Ser	Gly	Asp	Glu :	Met 475	Val	Ser	Leu	Lys	Asp 480
Tyr	Cys	Thr	Arg	Met 485	Lys	Glu	Asn	Gln	Lув 490	His	Ile	Tyr	Phe	Ile 495	Thr
Gly	Glu	Thr	Lys 500	Asp	Gln	Val	Ala	Asn 505	Ser	Ala	Phe	Val	Glu 510	Arg	Leu
Arg	Lys	His 515	Gly	Leu	Glu	Val	Ile 520	Tyr	Met	Ile	Glu	Pro 525	Ile	Asp	Glu
Tyr	Cys 530	Val	Gln	Gln	Leu	Lys 535	Glu	Phe	Glu	Gly	Lув 540	Thr	Leu	Val	Ser
Val 545	Thr	Lys	Glu	Gly	Leu 550	Glu	Leu	Pro	Glu	Asp 555	Glu	Glu	Glu	Lys	<b>Lys</b> 560
Lys	Gl.n	Glu	Glu	Гуs	ГÀЗ	Thr	Гув	Phe	Glu	Asn	Leu	Сув	Lуs	Ile	Met

285/299

565 570 575 Lys Asp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg 585 Leu Val Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr 600 Ala Asn Met Glu Arg Ile Ile Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp His Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg 680 Ile Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr Val Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp 725 <210> 324 <211> 725 <212> PRT <213> Gallus gallus <400> 324 Met Pro Glu Gln Val Gln His Gly Glu Asp Glu Val Glu Thr Phe Ala Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu Ile Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Ser Lys Leu Asp Thr Gly Lys Asp Leu Lys Ile Asp Ile Val Pro Asn Pro Arg Asp Pro Thr Leu Thr Leu Leu Asp Thr Gly Ile Gly Met Thr Lys Ala

Asp Leu Val Asn Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Lys Ala

			100					105					110		
Phe	Met	Glu 115	Ala	Leu	Gln	Ala	Gly 120	Ala	Asp	Ile	Ser	Met 125	Ile	Gly	Gln
Phe	Gly 130	Val	Gly	Phe	Tyr	Ser 135	Ala	Tyr	Leu	Val	Ala 140	Glu	Lys	Val	Val
Val 145	Ile	Thr	Lys	His	Asn 150	Asp	Asp	Glu	Gln	Tyr 155	Ala	Trp	Glu	Ser	Ser 160
Ala	Gly	Gly	Ser	Phe 165	Thr	Val	Arg	Thr	Asp 170	His	Gly	Glu	Pro	Ile 175	Gly
Arg	Gly	Thr	Lys 180	Val	Ile	Leu	Tyr	Leu 185	Lys	Glu	Asp	Gln	Thr 190	Glu	Tyr
Leu	Glu	Glu 195	Arg	Arg	Val	Lys	Glu 200	Val	Val	Lys	Lys	His 205	Ser	Gln	Phe
Ile	Gly 210	Tyr	Pro	Ile	Thr	Leu 215	Tyr	Val	Glu	ГÀЗ	Glu 220	Arg	Glu	Lys	Glu
Val 225	Ser	Asp	Asp	Glu	Ala 230	Glu	Glu	Glu	Lys	Val 235	Glu	Lys	Glu	Glu	Glu 240
Glu	Ser	Lys	Asp	Glu 245	Glu	Lys	Pro	Lys	Ile 250	Glu	Asp	Val	Gly	Ser 255	Asp
Glu	Glu	Glu	Glu 260	Glu	Gly	Glu	Lys	Ser 265	ГÀЗ	Lys	ГÀЗ	ГЛЗ	Thr 270	гЛа	Lys
Ile	Lys	Glu 275	Lys	Tyr	Ile	Asp	Gln 280	Glu	Glu	Leu	Asn	Lys 285	Thr	Lys	Pro
Ile	Trp 290	Thr	Arg	Asn	Pro	Asp 295	Asp	Ile	Thr	Gln	Glu 300	Glu	Tyr	Gly	Glu
Phe 305	Tyr	Lys	Ser	Leu	Thr 310	Asn	Asp	Trp	Glu	Asp 315	His	Leu	Ala	Val	Lys 320
His	Phe	Ser	Val	Glu 325	Gly	Gln	Leu	Glu	Phe 330	Arg	Ala	Leu	Leu	Phe 335	Ile
Pro	Arg	Arg	Ala 340	Pro	Phe	Asp	Leu	Phe 345	Glu	Asn	Lys	Lys	Lys 350	Lys	Asn
Asn	Ile	Lys 355	Leu	Tyr	Val	Arg	Arg 360	Val	Phe	Ile	Met	Asp 365	Ser	Cys	Asp
Glu	Leu 370	Ile	Pro	Glu	Tyr	Leu 375	Asn	Phe	Ile	Arg	Gly 380	Val	Val	Asp	Ser
Glu 385	Asp	Leu	Pro	Leu	Asn 390	Ile	Ser	Arg	Glu	Met 395	Leu	Gln	Gln	Ser	Lys 400
Ile	Leu	Ьys	Val	Ile 405	Arg	Lys	Asn	Ile	Val 410	Lys	Lys	Cys	Leu	Glu 415	Leu

## 287/299

Phe Thr Glu Leu Ala Glu Asp Lys Glu Asn Tyr Lys Lys Phe Tyr Glu 425 Ala Phe Ser Lys Asn Leu Lys Leu Gly Ile His Glu Asp Ser Thr Asn Arg Lys Arg Leu Ser Glu Leu Leu Arg Tyr His Thr Ser Gln Ser Gly Asp Glu Met Thr Ser Leu Ser Glu Tyr Val Ser Arg Met Lys Glu Ser Gln Lys Ser Ile Tyr Tyr Ile Thr Gly Glu Ser Lys Glu Gln Val Ala Asn Ser Ala Phe Val Glu Arg Val Arg Lys Arg Gly Phe Glu Val Val 505 Tyr Met Thr Glu Pro Ile Asp Glu Tyr Cys Val Gln Gln Leu Lys Glu 520 Phe Asp Gly Lys Thr Leu Val Ser Val Thr Lys Glu Gly Leu Glu Leu 535 Pro Glu Asp Glu Glu Glu Lys Lys Asn Met Glu Glu Ser Lys Ala Lys 550 Phe Glu Thr Leu Cys Lys Leu Met Lys Glu Ile Leu Asp Lys Lys Val 565 570 Glu Lys Val Thr Ile Ser Asn Arg Leu Val Ser Ser Pro Cys Cys Ile 585 Val Thr Ser Thr Tyr Gly Trp Thr Ala Asn Met Glu Arg Ile Met Lys 600 Ala Gln Ala Leu Arg Asp Asn Ser Thr Met Gly Tyr Met Met Ala Lys Lys His Leu Glu Ile Asn Pro Asp His Pro Ile Val Glu Thr Leu Arg Gln Lys Ala Asp Ala Asn Lys Asn Asp Lys Ala Val Lys Asp Leu Val Val Leu Leu Phe Glu Thr Ala Leu Leu Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ser Asn Arg Ile Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Glu Val Ile Ala Glu Glu Ser Ser Ile Ala Pro Pro Asp Glu Ile Pro Pro Leu Glu Gly Asp Glu Asp Thr Ser Arg 710 715

288/299

Met Glu Glu Val Asp 725

<210> 325

<211> 233

<212> PRT

<213> Sarcophaga crassipalpis

<400> 325

Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Asp Lys Val Thr 1 5 10

Val Thr Ser Lys His Asn Asp Asp Glu Gln Tyr Ile Trp Glu Ser Ser 20 25 30

Ala Gly Gly Ser Phe Thr Val Lys Pro Asp Ser Ser Glu Pro Leu Gly 35 40 45

Arg Gly Thr Lys Ile Val Leu Tyr Ile Lys Glu Asp Gln Thr Glu Tyr 50 60

Leu Glu Glu Ser Lys Ile Lys Glu Ile Val Asn Lys His Ser Gln Phe 65 70 75 80

Ile Gly Tyr Pro Ile Lys Leu Leu Val Gln Lys Glu Arg Asp Gln Glu
85 90 95

Val Ser Asp Asp Glu Ala Glu Glu Lys Lys Glu Met Asp Thr Asp 100 105 110

Glu Pro Lys Ile Glu Asp Val Gly Glu Asp Glu Asp Ala Asp Lys Lys
115 120 125

Asp Lys Asp Gly Lys Lys Lys Thr Ile Lys Val Ala Tyr Thr Glu 130 135 140

Asp Glu Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp 145 150 155 160

Asp Ile Thr Gln Ala Glu Tyr Gly Asp Phe Tyr Lys Ser Leu Thr Asn 165 170 175

Asp Trp Glu Asp His Leu Ala Val Lys His Phe Pro Leu Lys Gly Gln
180 185 190

Leu Glu Phe Arg Ala Leu Leu Phe Ile Pro Arg Arg Thr Pro Phe Asp 195 200 205

Leu Phe Glu Asn Gln Lys Lys Arg Asn Asn Ile Lys Leu Tyr Val Pro 210 215 220

Arg Val Phe Ile Met Asp Asn Cys Glu 225 230

<210> 326

<211> 724

289/299

<212> PRT <213> Danio rerio

<400> 326

Met Pro Glu Glu Met Arg Gln Glu Glu Glu Ala Glu Thr Phe Ala Phe 1 5 10 15

Gln Ala Glu Ile Ala Gln Leu Met Ser Leu Ile Ile Asn Thr Phe Tyr
20 25 30

Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu Val Ser Asn Ala Ser Asp 35 40 45

Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Thr Lys Leu 50 55 60

Asp Ser Gly Lys Asp Leu Lys Ile Asp Ile Ile Pro Asn Val Gln Glu 65 70 75 80

Arg Thr Leu Thr Leu Ile Asp Thr Gly Ile Gly Met Thr Lys Ala Asp 85 90 95

Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Lys Ala Phe 100 105 110

Met Glu Ala Leu Gln Ala Gly Ala Asp Ile Ser Met Ile Gly Gln Phe 115 120 125

Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Glu Lys Val Thr Val 130 135 140

Ile Thr Lys His Asn Asp Asp Glu Gln Tyr Ala Trp Glu Ser Ser Ala 145 150 155 160

Gly Gly Ser Phe Thr Val Lys Val Asp His Gly Glu Pro Ile Gly Arg 165 170 175

Gly Thr Lys Val Ile Leu His Leu Lys Glu Asp Gln Thr Glu Tyr Ile 180 185 190

Glu Glu Lys Arg Val Lys Glu Val Val Lys Lys His Ser Gln Phe Ile 195 200 205

Gly Tyr Pro Ile Thr Leu Tyr Val Glu Lys Glu Arg Asp Lys Glu Ile 210 215 220

Ser Asp Asp Glu Ala Glu Glu Glu Lys Ala Glu Lys Glu Glu Lys Glu 225 230 235 240

Glu Glu Gly Glu Asp Lys Pro Lys Ile Glu Asp Val Gly Ser Asp Asp 245 250 255

Glu Glu Asp Thr Lys Asp Lys Asp Lys Lys Lys Lys Lys Lys Ile Lys 260 265 270

Glu Lys Tyr Ile Asp Gln Glu Glu Leu Asn Lys Thr Lys Pro Ile Trp 275 280 285

### 290/299

Thr Arg Asn Pro Asp Asp Ile Ser Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp Glu Asp His Leu Ala Val Lys His Phe 315 305 Ser Val Glu Gly Gln Leu Glu Phe Arg Ala Leu Leu Phe Ile Pro Arg Arg Ala Pro Phe Asp Leu Phe Glu Asn Lys Lys Lys Asn Asn Ile 340 Lys Leu Tyr Val Arg Arg Val Phe Ile Met Asp Asn Cys Glu Glu Leu 360 Ile Pro Glu Tyr Leu Asn Phe Ile Arg Gly Val Val Asp Ser Glu Asp 375 Leu Pro Leu Asn Ile Ser Arg Glu Met Leu Gln Gln Ser Lys Ile Leu 395 Lys Val Ile Arg Lys Asn Ile Val Lys Lys Cys Leu Glu Leu Phe Ala 410 Asp Val Ala Glu Asp Lys Asp Asn Tyr Lys Lys Phe Tyr Asp Ala Phe 425 Ser Lys Asn Leu Lys Leu Gly Ile His Glu Asp Ser Gln Asn Arg Arg Lys Leu Ser Glu Leu Leu Arg Tyr Gln Ser Ser Gln Ser Gly Tyr Glu Met Thr Ser Leu Thr Glu Tyr Val Ser Arg Met Lys Glu Asn Gln Lys Ser Ile Tyr Tyr Ile Thr Gly Glu Ser Lys Asp Gln Val Ala His Ser Ala Phe Val Glu Arg Val Cys Lys Arg Gly Phe Glu Val Leu Tyr Met Thr Glu Pro Ile Asp Glu Tyr Cys Val Gln Gln Leu Lys Asp Phe Asp Gly Lys Ser Leu Val Ser Val Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Asp Glu Lys Lys Lys Met Glu Glu Asp Lys Ala Lys Phe Glu Asn Leu Cys Lys Leu Met Lys Glu Ile Leu Asp Lys Lys Val Glu Lys 570 Val Thr Val Ser Asn Arg Leu Val Ser Ser Pro Cys Cys Ile Val Thr 580

Ser Thr Tyr Gly Trp Thr Ala Asn Met Glu Arg Ile Met Lys Ala Gln

291/299 595 600 605 Ala Leu Arg Asp Asn Ser Thr Met Gly Tyr Met Met Ala Lys Lys His 615 Leu Glu Ile Asn Pro Asp His Pro Ile Met Glu Thr Leu Arq Gln Lys 630 Ala Glu Ala Asp Lys Asn Asp Lys Ala Val Lys Asp Leu Val Ile Leu Leu Phe Glu Thr Ala Leu Leu Ser Ser Gly Phe Ser Leu Asp Asp Pro Gln Thr His Ser Asn Arg Ile Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Glu Asp Val Pro Val Glu Glu Pro Ser Ser Ala Ala Pro Glu Asp Ile Pro Pro Leu Glu Gly Asp Asp Asp Ala Ser Arg Met 710 715 Glu Glu Val Asp <210> 327 <211> 722 <212> PRT <213> Salmo salar <400> 327 Met Pro Glu Glu Met Arg Gln Glu Glu Glu Ala Glu Thr Phe Ala Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu Ile Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Thr Lys Leu Asp Asn Gly Lys Glu Leu Lys Ile Asp Val Ile Pro Asn Val Glu Glu Arg Thr Leu Thr Leu Ile Asp Thr Gly Ile Gly Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile Ser Met Ile Gly Gln Phe 120

Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Glu Arg Val Thr Val

135

Ile 145	Thr	Lys	His	Asn	Asp 150	Asp	Glu	Gln	Tyr	Ile 155	Trp	Glu	Ser	Ser	Ala 160
Gly	Gly	Ser	Phe	Thr 165	Val	Lys	Val	Asp	Thr 170	Gly	Glu	Pro	Met	Leu 175	Arg
Gly	Thr	Lys	Val 180	Ile	Leu	His	Met	Ьув 185	Glu	Asp	Gln	Thr	Glu 190	Tyr	Val
Glu	Glu	Lys 195	Arg	Val	Lys	Glu	Val 200	Val	Lys	Lys	His	Ser 205	Gln	Phe	Ile
Gly	Tyr 210	Pro	Ile	Thr	Leu	Phe 215	Val	Glu	Lys	Glu	Arg 220	Glu	ьуs	Glu	Ile
Ser 225	Asp	Asp	Glu	Glu	Glu 230	ГÀв	Ala	Glu	Glu	Glu 235	ГÀЗ	Glu	Glu	Lys	Glu 240
Ala	Glu	Asp	Lys	Pro 245	Lys	Ile	Glu	Asp	Val 250	Gly	Ser	Asp	Asp	Glu 255	Glu
Asp	Ser	Ьуs	Asp 260	Lys	Asp	Lys	Lys	Ľуs 265	Thr	Lys	Lys	Ile	Lys 270	Glu	Lys
Tyr	Ile	Asp 275	Gln	Glu	Glu	Leu	Asn 280	Lys	Thr	Lys	Pro	Ile 285	Trp	Thr	Arg
Asn	Pro 290	Asp	Asp	Ile	Thr	Met 295	Glu	Glu	Tyr	Gly	Glu 300	Phe	Tyr	Lys	Ser
Leu 305	Thr	Asn	Asp	Trp	Glu 310	Glu	His	Leu	Ala	Val 315	ГÀЗ	His	Phe	Ser	Val 320
Glu	Gly	Gln	Leu	Glu 325	Phe	Arg	Ala	Leu	Leu 330	Phe	Ile	Pro	Arg	Arg 335	Ala
Pro	Phe	Asp	Leu 340	Phe	Glu	Asn	ГЛЗ	Lys 345	ГЛЗ	ГЛЗ	Asn	Asn	Ile 350	ràs	Leu
Tyr	Val	Arg 355	Arg	Val	Phe	Ile	Met 360	Asp	Ser	Cys	Glu	Glu 365	Leu	Ile	Pro
Glu	Tyr 370	Leu	Asn	Phe	Val	Arg 375	Gly	Val	Val	Asp	Ser 380	Glu	Asp	Leu	Pro
Leu 385	Asn	Ile	Ser	Arg	Glu 390	Met	Leu	Gln	Gln	Ser 395	Lys	Ile	Leu	Lys	Val 400
Ile	Arg	Lys	Asn	Ile 405	Val	Lys	Lys	Cys	Met 410	Glu	Leu	Phe	Gly	Glu 415	Leu
Ala	Glu	Asp	Arg 420	Glu	Asn	Tyr	Asn	Lys 425	Phe	Tyr	Asp	Gly	Phe 430	Ser	ГÀЗ
Asn	Leu	Lys 435	Leu	Gly	Ile	His	Glu 440	Asp	Ser	Gln	Asn	Arg 445	Lys	Lys	Leu

### 293/299

Ser Glu Leu Leu Arg Tyr His Ser Ser Gln Ser Gly Asp Glu Leu Thr 450 455 460

Ser Leu Thr Glu Tyr Leu Thr Arg Met Lys Asp Asn Gln Lys Ser Ile 465 470 475 480

Tyr Tyr Ile Thr Gly Glu Ser Lys Asp Gln Val Ala Asn Ser Ala Phe 485 490 495

Val Glu Arg Val Arg Lys Arg Gly Phe Glu Val Leu Tyr Met Thr Glu 500 505 510

Pro Ile Asp Glu Tyr Cys Val Gln Gln Leu Lys Glu Phe Asp Gly Lys 515 520 525

Thr Leu Val Ser Val Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu 530 540

Glu Glu Lys Lys Lys Met Asp Glu Asp Lys Thr Lys Phe Glu Asn Leu 545 550 560

Cys Lys Leu Met Lys Glu Ile Leu Asp Lys Lys Val Glu Lys Val Thr 565 570 575

Val Ser Asn Arg Leu Val Ser Ser Pro Cys Cys Ile Val Thr Ser Thr 580 585 590

Tyr Gly Trp Thr Ala Asn Met Glu Arg Ile Met Lys Ala Gln Ala Leu 595 600 605

Arg Asp Asn Ser Thr Met Gly Tyr Met Met Ala Lys Lys His Leu Glu 610 620

Ile Asn Pro Asp His Pro Ile Val Glu Thr Leu Arg Gln Lys Ala Asp 625 630 635 640

Leu Asp Lys Asn Asp Lys Ala Val Lys Asp Leu Val Ile Leu Leu Phe 645 650 655

Glu Thr Ala Leu Leu Ser Ser Gly Phe Ser Leu Asp Asp Pro Gln Thr  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670 \hspace{1.5cm}$ 

His Ser Asn Arg Ile Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp 675 680 685

Asp Asp Glu Val Ile Pro Glu Glu Pro Thr Ser Ala Pro Ala Pro Asp 690 695 700

Glu Ile Pro Pro Leu Glu Gly Asp Asp Asp Ala Ser Arg Met Glu Glu 705 710 715 720

Val Asp

<210> 328

<211> 733

<212> PRT

<213> Sus scrofa

294/299

<400> 328 Met Pro Glu Glu Thr Gln Thr Gln Asp Gln Pro Met Glu Glu Glu Val Glu Thr Phe Ala Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu Ile Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ser Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu Ile Pro Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Asp Thr Gly Ile Gly Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys 105 Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Glu Lys Val Thr Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr Ala Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Thr Asp Thr Gly Glu Pro Met Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu Asp Gln Thr Glu Tyr Leu Glu Glu Arg Arg Ile Lys Glu Ile Val Lys 200 Lys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Phe Val Glu Lys 215 Glu Arg Asp Lys Glu Val Ser Asp Asp Glu Ala Glu Glu Lys Glu Asp Lys Glu Glu Glu Lys Glu Lys Glu Lys Glu Ser Glu Asp Lys Pro Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Glu Glu Lys Lys Asp Gly Asp Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln

Glu Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp

295

290

Ile 305	Thr	Asn	Glu	Glu	Tyr 310	Gly	Glu	Phe	Tyr	Lys 315	Ser	Leu	Thr	Asn	Asp 320
Trp	Glu	Asp	His	Leu 325	Ala	Val	Гуѕ	His	Phe 330	Ser	Val	Glu	Gly	Gln 335	Leu
Glu	Phe	Arg	Ala 340	Leu	Leu	Phe	Val	Pro 345	Arg	Arg	Ala	Pro	Phe 350	Asp	Leu
Phe	Glu	Asn 355	Arg	Lys	Lys	Lys	Asn 360	Asn	Ile	Lys	Leu	Tyr 365	Val	Arg	Arg
Val	Phe 370	Ile	Met	Asp	Asn	Cys 375	Glu	Glu	Leu	Ile	Pro 380	Glu	Tyr	Leu	Asn
Phe 385	Ile	Arg	Gly	Val	Val 390	Asp	Ser	Glu	Asp	Leu 395	Pro	Leu	Asn	Ile	Ser 400
Arg	Glu	Met	Leu	Gln 405	Gln	Ser	Lys	Ile	Leu 410	ГÀЗ	Val	Ile	Arg	Lys 415	Asn
Leu	Val	Lys	Lys 420	Cys	Leu	Glu	Leu	Phe 425	Thr	Glu	Leu	Ala	Glu 430	Asp	ГÀЗ
Glu	Asn	Tyr 435	Lys	Lys	Phe	Tyr	Glu 440	Gln	Phe	Ser	Lys	Asn 445	Ile	r T	Leu
Gly	Ile 450	His	Glu	Asp	Ser	Gln 455	Asn	Arg	Lys	Lys	Leu 460	Ser	Glu	Leu	Leu
Arg 465	Tyr	Tyr	Thr	Ser	Ala 470	Ser	Gly	Asp	Glu	Met 475	Val	Ser	Leu	Lys	Asp 480
Tyr	Cys	Thr	Arg	Met 485	Lys	Glu	Asn	Gln	Lys 490	His	Ile	Tyr	Tyr	Ile 495	Thr
Gly	Glu	Thr	Lys 500	Asp	Gln	Val	Ala	Asn 505	Ser	Ala	Phe	Val	Glu 510	Arg	Leu
Arg	Lys	His 515	Gly	Leu	Glu	Val	Ile 520	Tyr	Met	Ile	Glu	Pro 525	Ile	Asp	Glu
Tyr	Сув 530	Val	Gln	Gln	Leu	Lys 535	Glu	Phe	Glu	Gly	Lys 540	Thr	Leu	Val	Ser
Val 545	Thr	Lys	Glu	Gly	Leu 550	Glu	Leu	Pro	Glu	Asp 555	Glu	Glu	Glu	Lys	Lуз 560
Lys	Gln	Glu	Glu	Lys 565	Lys	Thr	Lys	Phe	Glu 570	Asn	Leu	Cys	Lys	Ile 575	Met
Lys	Asp	Ile	Leu 580	Glu	Lys	Lys	Val	Glu 585	Lys	Val	Val	Val	Ser 590	Asn	Arg
Leu	Val	Thr 595	Ser	Pro	Cys	Cys	Ile 600	Val	Thr	Ser	Thr	Tyr 605	Gly	Trp	Thr

296/299

Ala Asn Met Glu Arg Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser 610 615 620

Thr Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp 625 630 635 640

His Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn 645 650 655

Asp Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu 660 665 670

Leu Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg 675 680 685

Ile Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro 690 695 700

Thr Ala Asp Asp Ser Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu 705 710 715 720

Glu Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp
725 730

<210> 329

<211> 709

<212> PRT.

<213> Saccharomyces cerevisiae

<400> 329

Met Ala Ser Glu Thr Phe Glu Phe Gln Ala Glu Ile Thr Gln Leu Met 1 5 10 15

Ser Leu Ile Ile Asn Thr Val Tyr Ser Asn Lys Glu Ile Phe Leu Arg 20 25 30

Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu Asp Lys Ile Arg Tyr Lys 35 40 45

Ser Leu Ser Asp Pro Lys Gln Leu Glu Thr Glu Pro Asp Leu Phe Ile 50 55 60

Arg Ile Thr Pro Lys Pro Glu Gln Lys Val Leu Glu Ile Arg Asp Ser 65 70 75 80

Gly Ile Gly Met Thr Lys Ala Glu Leu Ile Asn Asn Leu Gly Thr Ile 85 90 95

Ala Lys Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Ser Ala Gly Ala
100 105 110

Asp Val Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Leu Phe 115 120 125

Leu Val Ala Asp Arg Val Gln Val Ile Ser Lys Ser Asn Asp Asp Glu 130 140

Gln 145	Tyr	Ile	Trp	Glu	Ser 150	Asn	Ala	Gly	Gly	Ser 155	Phe	Thr	Val	Thr	Leu 160
Asp	Glu	Val	Asn	Glu 165	Arg	Ile	Gly	Arg	Gly 170	Thr	Ile	Leu	Arg	Leu 175	Phe
Leu	Lys	Asp	Asp 180	Gln	Leu	Glu	Tyr	Leu 185	Glu	Glu	Lys	Arg	Ile 190	Lys	Glu
Val	Ile	Lys 195	Arg	His	Ser	Glu	Phe 200	Val	Ala	Tyr	Pro	Ile 205	Gln	Leu	Val
Val	Thr 210	Lys	Glu	Val	Glu	Lys 215	Glu	Val	Pro	Ile	Pro 220	Glu	Glu	Glu	Lys
Lys 225	Asp	Glu	Glu	Lys	Lys 230	Asp	Glu	Glu	Lys	Lys 235	Asp	Glu	Asp	Asp	Lуs 240
Lys	Pro	Lys	Leu	Glu 245	Glu	Val	Asp	Glu	Glu 250	Glu	Glu	Lys	Lys	Pro 255	Lys
Thr	Гув	Lys	Val 260	Lys	Glu	Glu	Val	Gln 265	Glu	Ile	Glu	Glu	Leu 270	Asn	Lуs
Thr	Lys	Pro 275	Leu	Trp	Thr	Arg	Asn 280	Pro	Ser	Asp	Ile	Thr 285	Gln	Glu	Glu
Tyr	Asn 290	Ala	Phe	Tyr	Lys	Ser 295	Ile	Ser	Asn	Asp	Trp 300	Glu	Asp	Pro	Leu
Tyr 305	Val	Lys	His	Phe	Ser 310	Val	Glu	Gly	Gln	Leu 315	Glu	Phe	Arg	Ala	Ile 320
Leu	Phe	Ile	Pro	Lys 325	Arg	Ala	Pro	Phe	Asp 330	Leu	Phe	Glu	Ser	Lys 335	Lys
Lys	Lys	Asn	Asn 340	Ile	Lys	Leu	Tyr	Val 345	Arg	Arg	Val	Phe	Ile 350	Thr	Asp
Glu	Ala	Glu 355	Asp	Leu	Ile	Pro	Glu 360	Trp	Leu	Ser	Phe	Val 365	ГÀЗ	Gly	Val
Val	Asp 370	Ser	Glu	Asp	Leu	Pro 375	Leu	Asn	Leu	Ser	Arg 380	Glu	Met	Leu	Gln
Gln 385	Asn	Lys	Ile	Met	Lys 390	Val	Ile	Arg	Lys	Asn 395	Ile	Val	Lys	Lys	Leu 400
Ile	Glu	Ala	Phe	Asn 405	Glu	Ile	Ala	Glu	Asp 410	Ser	Glu	Gln	Phe	Glu 415	Lys
Phe	Tyr	Ser	Ala 420	Phe	Ser	Lys	Asn	Ile 425	Lys	Leu	Gly	Val	His 430	Glu	Asp
Thr	Gln	Asn 435	Arg	Ala	Ala	Leu	Ala 440	Lys	Leu	Leu	Arg	Tyr 445	Asn	Ser	Thr
Lys	Ser	Val	Asp	Glu	Leu	Thr	Ser	Leu	Thr	Asp	Tyr	Val	Thr	Arg	Met

298/299

450 455 460

Pro Glu His Gln Lys Asn Ile Tyr Tyr Ile Thr Gly Glu Ser Leu Lys 465 470 475 480

Ala Val Glu Lys Ser Pro Phe Leu Asp Ala Leu Lys Ala Lys Asn Phe
485 490 495

Glu Val Leu Phe Leu Thr Asp Pro Ile Asp Glu Tyr Ala Phe Thr Gln
500 505 510

Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Asp Ile Thr Lys Asp Phe 515 520 525

Glu Leu Glu Glu Thr Asp Glu Glu Lys Ala Glu Arg Glu Lys Glu Ile 530 535 540

Lys Glu Tyr Glu Pro Leu Thr Lys Ala Leu Lys Glu Ile Leu Gly Asp 545 550 560

Gln Val Glu Lys Val Val Val Ser Tyr Lys Leu Leu Asp Ala Pro Ala 565 570 575

Ala Ile Arg Thr Gly Gln Phe Gly Trp Ser Ala Asn Met Glu Arg Ile 580 590

Met Lys Ala Gln Ala Leu Arg Asp Ser Ser Met Ser Ser Tyr Met Ser 595 600 605

Ser Lys Lys Thr Phe Glu Ile Ser Pro Lys Ser Pro Ile Ile Lys Glu 610 620

Leu Lys Lys Arg Val Asp Glu Gly Gly Ala Gln Asp Lys Thr Val Lys 625 630 635 640

Asp Leu Thr Lys Leu Leu Tyr Glu Thr Ala Leu Leu Thr Ser Gly Phe 645 650 655

Ser Leu Asp Glu Pro Thr Ser Phe Ala Ser Arg Ile Asn Arg Leu Ile 660 665 670

Ser Leu Gly Leu Asn Ile Asp Glu Asp Glu Glu Thr Glu Thr Ala Pro 675 680 685

Glu Ala Ser Thr Ala Ala Pro Val Glu Glu Val Pro Ala Asp Thr Glu 690 695 700

Met Glu Glu Val Asp

<210> 330

<211> 260

<212> PRT

<213> Rana esculenta

<400> 330

Glu Met Ala Ser Leu Ser Glu Tyr Val Ser Arg Met Lys Glu Thr Gln

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Lys	Ser	Ile	Tyr 20	Tyr	Ile	Thr	Gly	Glu 25	Ser	ГÀЗ	Glu	Gln	Val 30	Ala	Asn
Ser	Ala	Phe 35	Val	Glu	Arg	Val	Arg 40	Lys	Arg	Gly	Phe	Glu 45	Val	Val	Туг
Met	Thr 50	Glu	Pro	Ile	Asp	Glu 55	Tyr	Cys.	Val	Gln	Gln 60	Leu	Lys	Glu	Phe
Asp 65	Gly	Lys	Thr	Leu	Val 70	Ser	Val	Thr	Lys	Glu 75	Gly	Leu	Glu	Leu	Pro 80
Glu	Asp	Asp	Glu	Glu 85	Lys	Lys	Lys	Met	Glu 90	Glu	Asn	Lys	Thr	Lys 95	Phe
Glu	Gly	Leu	Cys 100	Lys	Leu	Met	Lys	Glu 105	Ile	Leu	Asp	Lys	Lys 110	Val	Glu
Lys	Val	Thr 115	Val	Ser	Asn	Arg	Leu 120	Val	Ser	Ser	Pro	Cys 125	Cys	Ile	Val
Thr	Ser 130	Thr	Tyr	Gly	Trp	Thr 135	Ala	Asn	Met	Glu	Arg 140	Ile	Met	ГÀЗ	Ala
Gln 145	Ala	Leu	Arg	Asp	Asn 150	Ser	Thr	Met	Gly	Tyr 155	Met	Met	Ala	Lys	Lys 160
His	Leu	Glu	Ile	Asn 165	Pro	Glu	His	Pro	Ile 170		Glu	Thr	Leu	Arg 175	Gln
Lys	Ala	Glu	Ala 180	Asp	Lys	Asn	Asp	Lys 185		Val	Lys	Asp	Leu 190	۷al	Val
Leu	Leu	Phe 195	Glu	Thr	Ala	Leu	Leu 200		Ser	Gly	Phe	Ser 205	Leu	Asp	Asp
Pro	Gln 210	Thr	His	Ser	Asn	Arg 215		Tyr	Arg	Met	Ile 220		Leu	Gly	Leu
Gly 225	Ile	Asp	Glu	Asp	Glu 230	Pro	Ala	Ile	Glu	Glu 235	Thr	Thr	Ala	Ala	Val 240
Pro	Asp	Asp	Ile	Pro 245		Leu	Glu	Gly	Glu 250		Asp	Ala	Ser	Arg 255	
Glu	Glu	Val	Asp 260												